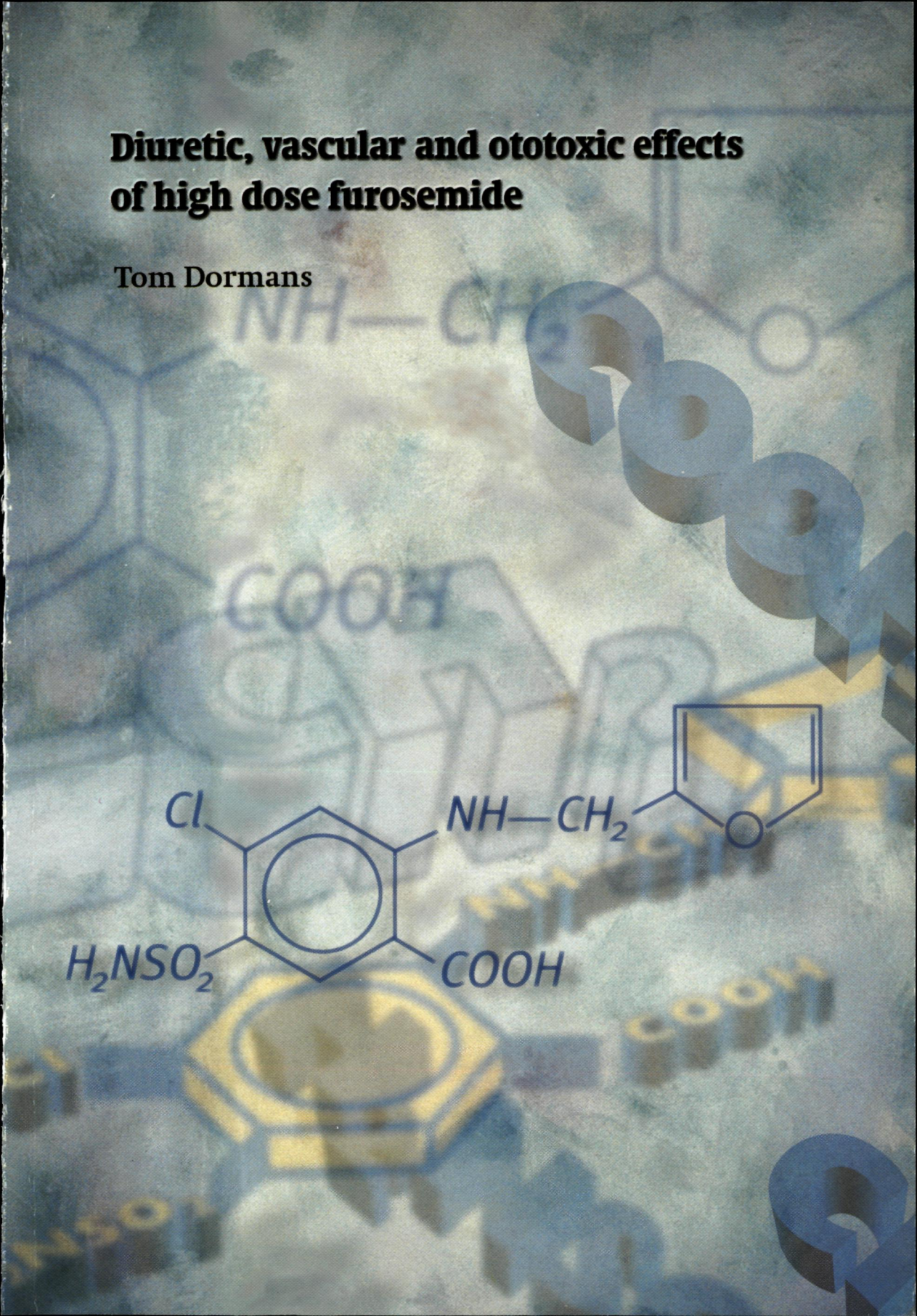
Diuretic, vascular and ototoxic effects of high dose furosemide

Tom Dormans



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CONTENTS

CHAPTER ONE

INTRODUCTION AND OUTLINE

Since their introduction into clinical practice almost 40 years ago, loop diuretics belong to the most widely prescribed drugs This class of drugs comprises ethacrynic acid, bumetanide, furosemide, and, not registered in The Netherlands, torasemide and piretanide This thesis will focus on furosemide Furosemide has shown to be effective in oedematous states associated with cardiac, renal and hepatic disease In the past thirty years the pharmacokinetic and pharmacodynamic properties of furosemide have been extensively studied in healthy persons as well as in various disease states [1,2]
In the treatment of chronic congestive heart failure the recommended daily dosage of furosemide is 20-200 mg [3] However, several studies have established the efficacy of daily dosages ranging from 250-4000 mg when recommended dosages fail to reduce the excess of body fluid to the desired level in both renal failure and heart failure These supra-conventional dosages are often referred to as high dose furosemide

In this thesis three aspects of the use of high dose furosemide are sudied

Diuretic effects of high dose furosemide

Although the continuous intravenous infusion of high dose furosemide has some theoretical advantages above other modes of administration (improved efficacy, less toxic side effects), studies comparing this mode of administration with intravenous bolus injection(s) in patients with heart failure were contradictive [8,9] Moreover, in none of these reports the population consisted of patients with congestive heart failure unresponsive to conventional dosages of loop diuretics

When chronic heart failure progresses some patients appear to become non-responsive even to the use of high dose furosemide, irrespective of the mode of administration Whether there are any effective treatment options for these patients is unclear The treatment with positive inotropic drugs, such as dobutamine, occasionally has been employed successfully to restore the diuretic response to loop diuretics Other studies suggest that patients with congestive heart failure may benefit from extracorporal techniques like peritoneal dialysis or hemofiltration [10-18] However, in most of these studies the stage of heart failure is not well-defined or the extracorporal treatment modality was introduced before maximal conventional therapy, including high dose furosemide, was applied

When conventional dosages of loop diuretics are combined with thiazide drugs, this results in a vigorous natriuresis, even in patients with moderate renal failure [19-30] Whether the addition of a thiazide drug to high dose furosemide may cause a correction of the hydration status in patients with chronic decompensated heart failure (insufficiently responding to high dose furosemide) remains to be established

After chronic administration of furosemide, its natriuretic effects attenuate due to several mechanisms [31-40] Animal studies have shown that coadministration of a thiazide preserves the natriuretic response to furosemide [41] In literature little evidence is available for the presence of this interaction in humans [34]

In summary, the purpose of the studies described in this thesis, which focus on the diuretic aspects of high dose furosemide, was to answer the following questions

- *Is the use of high dose furosemide administered as an intravenous continuous infusion effective and safe in patients with severe congestive heart failure unresponsive to conventional dosages of furosemide?*

- *Does the efficacy of high dose furosemide in patients with severe heart failure improve when furosemide is administered as a continuous intravenous infusion compared to an intravenous bolus injection?*
- *Do patients with severe congestive heart failure and an inadequate response to high dose furosemide benefit from chronic intermittent hemodialysis and/or hemofiltration?*
- *Is the addition of hydrochlorothiazide to high dose furosemide of any value for patients with severe congestive heart failure and diuretic resistance to high dose furosemide?*
- *Can the attenuation of the natriuretic response that occurs after chronic use of furosemide be prevented by coadministration of hydrochlorothiazide?*

Vascular effects of high dose furosemide

It is generally recognized that loop diuretics provide relief of symptoms in acute left ventricular heart failure by its non-diuretic effects. Many studies have established that furosemide has vasoactive properties [42-49] The exact mechanisms involved in the vasoactivity of furosemide are unclear. Most studies so far failed to make a proper distinction between genuine direct vascular effects of furosemide versus effects on vascular tone secondary to cardiovascular reflexes or regulatory mechanisms. The application of techniques that can measure the effects of locally administered drugs on isolated vascular beds in vivo, enables us to answer the question whether furosemide acts directly on the vessel or induces indirect effects secondary to changes in intravascular volume and blood pressure.
The questions in this thesis concerning the vascular effects of furosemide are

- *Does furosemide exert any direct vascular effect in humans?*
- *If so, is it a vasodilator or a vasoconstrictor effect?*
- *On which part of the vasculature (venous or arterial) does furosemide act?*
- *If there is a direct vasoactive effect: is it mediated by prostaglandins or does NO, a potent vasodilator released by endothelial cells, play a role?*

Ototoxic side effects of high dose furosemide

In the early 1970's it was shown that high dose furosemide was an effective mode of treatment in patients with renal insufficiency or heart failure unresponsive to conventional dosages of loop diuretics. Soon after the introduction of high dose furosemide, ototoxicity was reported to be a major side effect of this therapy [50-54] Although in the majority of cases this ototoxicity was rapidly reversible, few reports described irreversible hearing loss, entirely attributable to the use furosemide [54-56]. In the past two decades many studies in animals have been performed to elucidate the mechanisms involved in ototoxic side effects of loop diuretics, but many questions remain to be answered. It was shown that the ototoxic side effects were related to the furosemide endolymph concentration, which appeared to be linearly related to the serum furosemide concentration within a wide range [57,58]. To our knowledge no data are available that describe the relationship between the pharmacokinetics and the ototoxicity of furosemide in humans. To clarify this relationship a study was performed aiming to answer the following questions:

- *Is it possible to avoid ototoxicity by administration of high dose furosemide as a continuous intra venous infusion instead of an intravenous bolus injection?*
- *If the serum furosemide concentration is the major determinant of the development of ototoxicity, is it possible to define a threshold furosemide concentration below which ototoxicity does not occur?*

References

1 Hammarlund Udenaes M and Benet LZ Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update J Pharmacokinet Biopharm 1989 17 1 46
2 Ponto LL and Schoenwald RD Furosemide (frusemide) A pharmacokinetic pharmacodynamic review (Part I) Clin Pharmacokinet 1990 18 381-408
3 Cohn JN The management of chronic heart failure N Engl J Med 1996 335 488 498
4 Cantarovich F Fernandez JC Locatelli A and Perez Toledo J Frusemide in high doses in the treatment of acute renal failure Postgrad Med J 1971 47 Suppl 13 Suppl 17
5 Gerlag PG and van Meijel JJ High dose furosemide in the treatment of refractory congestive heart failure Arch Intern Med 1988 148 286 291
6 Waterer G and Donaldson M High dose frusemide for cardiac failure Lancet 1995 346 254
7 Ritz E Elser D, Nowicki M and Stein G Treatment with high doses of loop diuretics in chronic renal failure Nephrol Dial Transplant 1994 9 Suppl 3 40 43
8 Copeland JG Campbell DW Plachetka JR Salomon NW and Larson DF Diuresis with continuous infusion of furosemide after cardiac surgery Am J Surg 1983 146 796 799
9 Lahav M Regev A Ramanani P and Theodor E Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure Chest 1992 102 725 731
10 Biasioli S Barbaresi I Barbieto M Pettosino I Cavallini I Zambello A et al Intermittent venovenous hemofiltration as a chronic treatment for refractory and intractable heart failure ASAIO J 1992 38 M658 M663
11 Agostoni PG Marenzi GC Pepi M Doria E Salvioni A Perego G et al Isolated ultrafiltration in moderate congestive heart failure J Am Coll Cardiol 1993 21 424 431
12 Inoue T Morooka S Hayashi I Takayanagi K Sakai Y Yamanaka T et al Effectiveness of continuous arteriovenous hemofiltration for patients with refractory heart failure Jpn Heart J 1988 29 595-602
13 Chapman A Rotelli C Mackow RC and Hanson K Continuous arteriovenous hemofiltration in patients with severe congestive heart failure Am J Med 1987 83 1167 1168
14 Rimondini A Cipolla CM Della Bella P Grazi S Sisillo E Susini G et al Hemofiltration as short term treatment for refractory congestive heart failure Am J Med 1987 83 43 48
15 L'Abbate A Emdin M Placenti M Panichi V Biagini A Clerico A et al Ultrafiltration a rational treatment for heart failure Cardiology 1989 76 384 390
16 Simpson IA Rae AP Simpson K Gribben J Boulton Jones JM Allison MF et al Ultrafiltration in the management of refractory congestive heart failure Br Heart J 1986 55 344-347
17 Agostoni P Marenzi G Lauri G Perego G Schianni M Sganzerla P et al Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency failure of furosemide to provide the same result Am J Med 1994 96 191 199
18 Inoue T Sakai Y Morooka S Takayanagi K Hayashi I and Takabatake Y Hemofiltration as treatment for patients with refractory heart failure Clin Cardiol 1992 15 514-518
19 Gunstone RT Wing AJ Shani HG Njemo D and Sabuka FM Clinical experience with metolazone in fifty two African patients synergy with frusemide Postgrad Med J 1971 47 789 793
20 Epstein MR Lepp BA Hoffman A and Levinson R Potentiation of furosemide by metolazone in refractory edema Curr Ther Res 1977 21 656 667
21 Wollam GL Tarazi RC Bravo EL and Dustan HP Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia Am J Med 1982 72 929 938
22 Ghose RR and Gupta SK Synergistic action of metolazone with "loop" diuretics Br Med J Clin Res Ed 1981 282 1432 1433
23 Channer KS McLean KA Lawson Matthew P and Richardson M Combination diuretic treatment in severe heart failure a randomised controlled trial Br Heart J 1994 71 146 150
24 Kiyingi A Field MJ Pawsey CC Yiannikas J Lawrence JR and Arter WJ Metolazone in treatment of severe refractory congestive cardiac failure Lancet 1990 335 29 31
25 Brater DC Pressley RH and Anderson SA Mechanisms of the synergistic combination of metolazone and bumetanide J Pharmacol Exp Ther 1985 233 70 74
26 Brown E and MacGregor G Synergistic action of metolazone and frusemide Br Med J Clin Res Ed 1981 283 1611
27 Aravot DJ Banner NR Musumeci F Fitzgerald M Madden B Khaghani A et al Oral metolazone plus frusemide for home therapy in patients with refractory heart failure Lancet 1989 727 728
28 Elser D Schroter M Neubeck M and Ritz E Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure Kidney Int 1994 46 482 488
29 Knauf H and Mutschler E Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure J Cardiovasc Pharmacol 1995 26 394-400
30 Knauf H and Mutschler E Functional state of the nephron and diuretic dose-response—rationale for low-dose combination therapy Cardiology 1994 84 Suppl 2 18 26
31 Wilcox CS Mitch WL Kelly RA Skorecki K Meyer TW Friedman PA et al Response of the kidney to furosemide I Effects of salt intake and renal compensation J Lab Clin Med 1983 102 450 458
32 Kelly RA Wilcox CS Mitch WL Meyer TW Souney PF Rayment CM et al Response of the kidney to furosemide II Effect of captopril on sodium balance Kidney Int 1983 24 233-239
33 Sjostrom P Mechanisms of reduced effects of loop diuretics in healthy volunteers and in patients with renal disease Scand J Urol Nephrol Suppl 1988 111 1 66
34 Loon NR Wilcox CS and Unwin RJ Mechanism of impaired natriuretic response to furosemide during prolonged therapy Kidney Int 1989 36 682-689
35 Brater DC Resistance to loop diuretics Why it happens and what to do about it Drugs 1985 30 427 443
36 Brater DC Diuretic resistance mechanisms and therapeutic strategies Cardiology 1994,84 Suppl 2 57 67
37 Ellison DH The physiologic basis of diuretic synergism its role in treating diuretic resistance Ann Intern Med 1991 114 886 894
38 Ellison DH Velazquez H and Wright FS Adaptation of the distal convoluted tubule of the rat Structural and functional effects of dietary salt intake and chronic diuretic infusion J Clin Invest 1989 83 113 126
39 Ellison DH Diuretic drugs and the treatment of edema from clinic to bench and back again Am J Kidney Dis 1994 23 623-643
40 Ellison DH Pusschett JB Greenberg A editors Diuretics IV Chemistry Pharmacology and Clinical Applications Amsterdam Elsevier Science Publishers BV 1993 1 Epithelial cell hypertrophy a physiological cause of diuretic resistance 427 434
41 Morsing P Velazquez H Wright FS and Ellison DH Adaptation of distal convoluted tubule of rats II Effects of chronic thiazide infusion Am J Physiol 1991 261 F137 F143
42 Dikshit K Vyden JK Forrester JS Chatterjee K Prakash R and Swan HJ Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction N Engl J Med 1973 288 1087 1090

43 Ikram H Chan W I spiner FA and Nicholls MG Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure Clin Sci 1980 59 443 449
44 Francis GS Siegel RM Goldsmith SR Olivari MT Levine TB and Cohn JN Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure Activation of the neurohumoral axis Ann Intern Med 1985 103 1-6
45 Passmore AP Whitehead FM and Johnston GD Comparison of the acute renal and peripheral vascular responses to frusemide and bumetanide at low and high dose Br J Clin Pharmacol 1989 27 305 312
46 Johnston GD Nicholls DP Kondowe GB and Finch MB Comparison of the acute vascular effects of frusemide and bumetanide Br J Clin Pharmacol 1986 21 359 364
47 Johnston GD Hiatt WR Nies AS Payne NA Murphy RC and Gerber JG Factors modifying the early nondiuretic vascular effects of furosemide in man The possible role of renal prostaglandins Circ Res 1983 53 630-635
48 Johnston GD Nicholls DP and Feahey WJ The dose response characteristics of the acute non diuretic peripheral vascular effects of frusemide in normal subjects Br J Clin Pharmacol 1984 18 75 81
49 Mukherjee SK Katz MA Michael UF and Ogden DA Mechanisms of hemodynamic actions of furosemide differentiation of vascular and renal effects on blood pressure in functionally anephric hypertensive patients Am Heart J 1981 101 313-318
50 Cooperman LB and Rubin II Toxicity of ethacrynic acid and furosemide Am Heart J 1973 85 831 834
51 Schwartz GH David DS Riggio RR Stenzel KH and Rubin AI Ototoxicity induced by furosemide N Engl J Med 1970 282 1413 1414
52 Heidland A and Wigand ML Hearing loss induced by the use of high doses of furosemide in the treatment of uremia J Klin Wochenschr 1970 48 1052 1056
53 Venkateswaran PS Transient deafness from high doses of frusemide Br Med J 1971 4 113 114
54 Lloyd Mostyn RH and Lord IJ Ototoxicity of intravenous frusemide Lancet 1971 2 1156
55 Quick CA and Hoppe W Permanent deafness associated with furosemide administration Ann Otol Rhinol Laryngol 1975 84 94-101
56 Gallagher KJ and Jones JK Furosemide-induced ototoxicity Ann Intern Med 1979 91 744-745
57 Brustlow SW Propranolol antagonism to the effect of furosemide on the composition of endolymph in guinea pigs Can J Physiol Pharmacol 1976 54 42-48
58 Green IP Rybak IP Mirkin BI Juhn SKandMorizono I Pharmacologic determinants of ototoxicity of furosemide in the chinchilla J Pharmacol Exp Ther 1981 216 537 542

CONTINUOUS INFUSION OF FUROSEMIDE IN THE TREATMENT OF PATIENTS WITH CONGESTIVE HEART FAILURE AND DIURETIC RESISTANCE

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ABSTRACT

Objectives: To assess the value of treatment with continuous intravenous infusion of furosemide in patients with refractory congestive heart failure

Design: Open uncontrolled dose response study

Subjects: Patients with congestive heart failure (those with New York Heart Association (NYHA) class III and IV with an assessed amount of oedema of more than 5 kg and diuretic resistance were included [n=10]) Diuretic resistance was defined as failure to lose weight and/or inappropriate urinary sodium excretion (50 mmol 24 h') despite bed rest for a period of 2-3 days, salt and water restriction, orally and intravenously administered furosemide in a dose of 250 mg day', digoxin, and when possible an ACE inhibitor Included patients were treated with continuous furosemide infusion at a delivery of 20 mg h over 24 h The infusion rate was gradually heightened up to a maximum dose of 160 mg h'

Main outcome measures: Daily physical examination, history of side effects, determination of serum electrolytes and 24 h electrolyte excretion during treatment with furosemide

Results: Weight loss (mean ±SD), 12 5 ±5 kg) and relief of symptoms was achieved in all patients Mean (±SD) 24 h sodium output rose from 19 ±16 mmol 24 h' (n=10) on oral therapy with 250 mg congestive heart failure to 137 ±85 mmol 24 h' (n=8) during 80 mg h and to 268 ±124 mmol 24 h (n=3) on the maximal dose of 160 mg h'

Conclusion: Continuous infusion of furosemide under careful monitoring of the patient is a safe, controllable and efficient treatment in patients with severe congestive heart failure and diuretic resistance

INTRODUCTION

Despite the important role of ACE inhibitors, diuretics remain the mainstay treatment for patients with congestive heart failure especially when fluid retention dominates [1] Conventional diuretic therapy consists of a loop diuretic either as one or multiple oral doses or as an intravenous bolus dose [2] Most patients will respond with sufficient natriuresis, weight decrease and clinical improvement to this regimen However, some patients with severe congestive heart failure show diuretic resistance with an inadequate diuretic response as a consequence Diuretic resistance is a serious problem in these patients and seems to represent a final manifestation of congestive heart failure [3] When resistance to loop diuretics develops, combination therapy with a diuretic that exerts its action in another part of the nephron tubule could be successful [3,4] However, it must be stressed that severe electrolyte disturbances can ensue when a combination of different diuretics is used Other therapeutic interventions, especially appropriate for patients with severe renal impairment, could be hemofiltration or infusion with positive inotropic agents (e g dopamine and dobutamine) [5,6] High bolus doses of a loop diuretic are successful, but may be ototoxic [7,8] Also, continuous intravenous infusion of a loop diuretic -to make optimal use of its diuretic properties has been advocated [4,9-11] From a theoretical point of view, continuous infusion of a loop diuretic may have two important advantages Firstly, the diuretic efficiency is optimal when there is a constant delivery rate of furosemide to the proximal tubule and secondly, plasma furosemide levels remain relatively low making ototoxic side effects less probable Up until now there are a few data regarding the efficacy of continuous furosemide infusion therapy in patients with refractory congestive heart failure Therefore, we conducted a study in patients with severe congestive heart failure and diuretic resistance, investigating the pharmacokinetic and pharmacodynamic determinants of response during continuous furosemide infusion

Patient	Age (years) /sex	Weight (kg) decomp	Weight decrease (kg)	Cl_{cr} (ml.min^{-1}) decomp	Cl_{cr} (ml.min^{-1}) comp	NYHA decomp	NYHA comp	Diagnosis	EF(%)	Other medication	Maximal F Dose (mg.24h^{-1})
1	64/m	88.2	18.5	40	43	IV	II	CAD	15	C,D,K,T	3840
2	80/f	63.1	16.6	36	33	IV	III	CC	18	D,K	3840
3	84/m	43.7	6.6	15	13	IV	III	CAD	20	D,K	3840
4	68/f	61.1	10.8	37	23	III	II	CAD	35	C,D,I,T	1920
5	59/m	82.5	11	23	28	IV	III	PH	17	C,D,K,I	2880
6	76/m	81.1	19.1	26	30	IV	III	CAD	15	C,D,T,Am	1920
7	82/m	79.6	7.6	41	50	IV	III	CP	19	C,D,A	960
8	71/m	84.3	6.3	40	44	IV	III	CAD	28	D,D	1920
9	73/f	62.8	7.4	59	47	IV	III	CAD	17	D,K,Th	480
10	57/m	78.3	17.3	48	45	IV	III	CAD	26	C,D,K	2880
Mean	71.4	72.3	12.0	36	36				21.0		
SEM	3.0	4.5	1.7	6	6				2.1		

Table 1. *Characteristics of patients with refractory failure before (decompensated) and after (compensated) treatment with continuous infusion of furosemide*

Abbreviations A= acenocoumarol Am= amiodarone C = captopril, CAD= coronary artery disease, CC= congestive cardiomyopathy, Cl_{cr}= creatinine clearance, comp= compensated, CP= coronary pulmonale D= digoxin, decomp= decompensated, EF= ejection fraction I = furosemide, I= isosorbidedinitrate= K= K diuretic, NYHA= New York Heart Association, PH= pulmonary hypertension, T = tolbutamide Th= theophylin

PATIENTS AND METHODS

After approval of the protocol by the local ethical committee, we selected patients with severe congestive heart failure (NYHA III-IV) of different origins with a proven diuretic resistance and an assessed amount of oedema of more than 5 kg. Diuretic resistance was defined as a failure to lose weight and/or inappropriate urinary sodium excretion (< 50 mmol 24 h^{-1}) despite maximal conventional therapy i.e. bed rest for 2-3 days, salt and water restriction, orally and intravenously administered furosemide in a dose of 250 mg day^{-1}, digoxin, and when possible an ACE inhibitor. The relevant patient characteristics are shown in Table 1: the mean age was 71.4 (range 57-84) years and the mean weight was 72.3 (range 43.7-88.2) kg. The patients were given a physical examination, complete blood count, electrocardiogram, echocardiogram and chest X-ray and all gave their written informed consent prior to the study.

Continuous intravenous furosemide infusion treatment was started by an automatic syringe infusion pump (type STC 521, Terumo Corporation, Tokyo, Japan) with 480 mg 24 h^{-1} (infusion rate 20 mg h^{-1}). Furosemide medication in the infusion pump was protected against light. We heightened the furosemide infusion rate gradually when patients did not show weight loss or if there was no enhancement of diuresis or natriuresis after 24 h. The maximal furosemide infusion rate was 160 mg h^{-1} (cumulative dose 3840 mg 24 h^{-1}). During their stay in the hospital, the patients received a diet containing 60-80 mmol sodium and 80-100 mmol potassium. Total daily fluid intake was limited to 1500 ml. Additional medication (e.g. digoxin, captopril) was permitted and not changed during treatment with continuous furosemide infusion. Every day, all of the patients were physically examined by the same physician. Continuous infusion was stopped when patients were clinically compensated. At that time, oral furosemide administration was started at a dose of 250 mg. In most cases, the dose required to control recurrent oedema had to be gradually increased (maximally up to 500 mg b.i.d.) during follow-up.

Daily 24 h urine collection was carried out and the urine samples were carefully protected from light. Aliquots of the urine samples were assayed immediately for sodium, potassium, chloride, albumin and creatinine content and the rest of the samples were frozen for later analysis of furosemide concentration. Venous blood samples were taken daily for determination of electrolytes, blood/urea nitrates, creatinine and plasma furosemide concentration. Also, venous blood samples were taken on the day of admission and 1 day before the patient left the hospital for determination of urate, bicarbonate, albumin, magnesium, aldosterone and renin. The concentrations of furosemide in plasma and urine were determined by a recently developed HPLC assay, with a solid-phase extraction method [12]. The plasma aldosterone and plasma renin concentrations were determined by radioimmunoassay [13,14]. Routine blood chemistry was measured by auto-analyser. Diuretic response was expressed as daily sodium excretion (mmol 24 h^{-1}) or as fractional sodium excretion (FE_{Na}), defined as

$$FE_{Na}\,(\%) = \frac{U_{Na} \cdot Se_{Cr}}{Se_{Na} \cdot U_{Cr}}\ 100$$

where U_{Na} is the urinary sodium concentration (mmol l^{-1}), Se_{Cr} is the serum creatinine concentration (μmol l^{-1}), Se_{Na} is the serum sodium concentration (mmol l^{-1}) and U_{Cr} is the urinary creatinine concentration (mmol l^{-1}). Each symbol in the dose-response curve represents the mean (SEM) FE_{Na} calculated from 24 h urine collections on the day after heightening of the furosemide dose, and the corresponding furosemide dose.

A two-dimensional echocardiography was used to measure the left ventricular ejection fraction. Patients were daily interviewed about side effects. Values were expressed as mean ±SD) unless indicated otherwise.

RESULTS

The currently investigated patients were resistant to conventional diuretic treatment as demonstrated by the very low natriuresis (19 ±16 mmol 24 h^{-1} respectively 32 ±18 mmol 24 h^{-1}) despite therapy with 250 mg of furosemide orally respectively intravenously As shown in Table 1 the endogenous creatinine clearance was markedly reduced and the blood/urea nitrates creatinine (BUN/cr) ratio was high in all patients These parameters including the low ejection fractions (Table 1) demonstrate the deteriorated hemodynamic state of these patients The mean (±SD) 24 h sodium output rose from 19 ±16 mmol 24 h^{-1} (n=10) on oral therapy with 250 mg of furosemide to 137 ±85 mmol 24 h^{-1} (n=8) during 1920 mg 24 h^{-1} and to 268 ±124 mmol 24 h^{-1} (n=3) on the maximal administered dose of 3840 mg 24 h^{-1} (infusion rate 160 mg h^{-1}), whilst the mean daily potassium output rose from 50 ±21 mmol 24 h^{-1} to 78 ±41 and 82 ±50 mmol 24 h^{-1} respectively The mean duration of treatment was 13 ±5 days

Table 2 *Biochemical parameters of patients with congestive heart failure before (decompensated) and after (compensated) treatment with continuous furosemide infusion (n=10)*

	Decompensated		Compensated	
BUN/cr	30 6	±3 5	35 0	±4 2
Serum sodium (mmol l^{-1})	134	±2 1	138	±0 1
Serum potassium (mmol l^{-1})	4 3	±0 2	4 1	±0 2
Serum albumin (g l^{-1})	31	±2 5	32	±2 3
Serum urea (mmol l^{-1})	16	±1 7	18	±2 1
Serum bicarbonate (mmol l^{-1})	30 6	±2 4	32 3	±2 4
Serum urate (mmol l^{-1})	0 62	±0 04	0 66	±0 06
Serum magnesium (mmol l^{-1})	0 88	±0 04	0 98	±0 06
Renin (nmol l^{-1} h^{-1})	15 4	±5 4	15 0	±4 8
Aldosterone (mmol l^{-1})	1 5	±0 6	1 5	±0 5

Values are mean ±SEM
BUN/cr blood/urea nitrates creatinine ratio

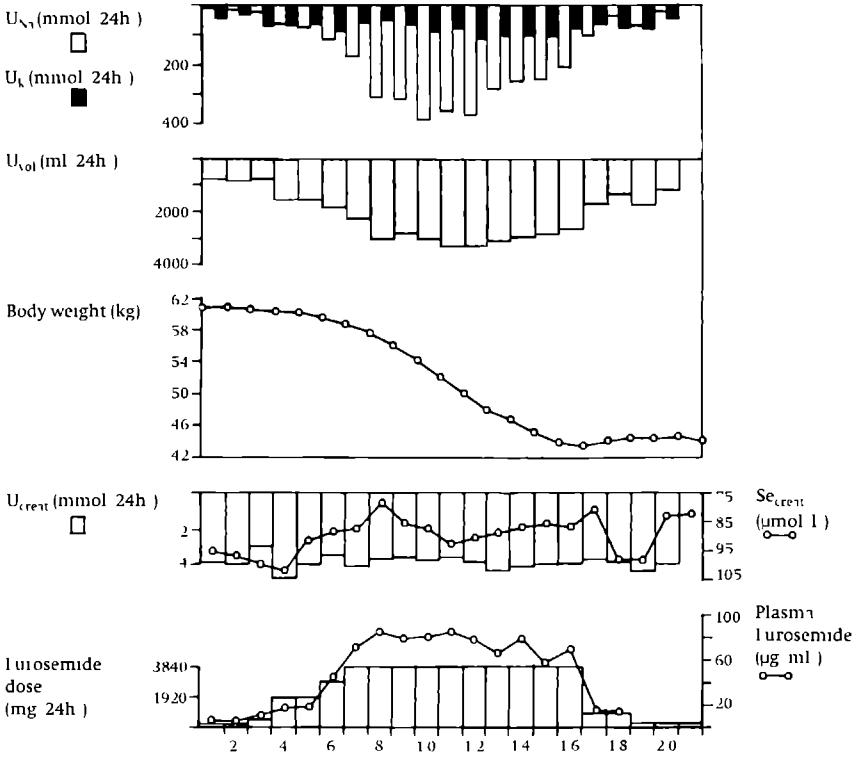
Figure 1 shows the daily urinary volume and electrolyte excretions and some biochemical parameters of one representative patient (no 2) Increasing the furosemide dose also increased volume and electrolyte excretions However when patients had almost reached the compensated state the responsiveness of the kidney to furosemide diminished with a lower natriuresis as a consequence In all patients an improvement of the state of compensation and a weight reduction was realized Mean weight reduction was 12 0 (range 6 3 19 1) kg Serum sodium concentrations gradually increased to normal values and a mild easy to treat hypokalemia occurred in almost all patients especially in those with hyperaldosteronism Otherwise no serious side effects were observed
Table 2 shows the biochemical parameters before and after continuous furosemide infusion when patients were decompensated and again when patients were compensated A small insignificant increase in the BUN/cr ratio and a small decrease in the mean arterial pressure (MAP) was observed (MAP ±SEM decompensated 82 ±3 5 mmHg compensated 78 ±3 4 mmHg) However, we did not find significant increases in the serum renin and in the aldosterone levels
Plasma furosemide levels averaged 4 3 ± 2 8 (range 2 6 5 8) µg ml^{-1} at the lowest infusion rate (10 mg h^{-1}) and increased to 71 1 ±33 3 (range 26 6 136 4) mg ml^{-1} at the highest infusion rate (160 mg h^{-1}) In one patient (no 3) furosemide plasma levels were in the ototoxic presumed range (> 100 mg ml^{-1}) but even in this patient no adverse effects were noticed

This was the patient with the lowest ECC, who was treated with the maximum furosemide infusion rate (160 mg h^{-1}). As shown in the dose-response relation (Figure 2) there is a positive correlation (r^2 = 0.958, p = 0.0004) between the furosemide dose and the fractional sodium excretion, indicating that higher furosemide doses induce greater natriuresis.

Discussion

Our study shows that continuous furosemide infusion is an applicable, effective and safe treatment in patients with severe congestive heart failure and diuretic resistance. Diuretic resistance in patients with severe congestive heart failure is a multi-causal phenomenon and seems to be determined by pharmacokinetic as well as pharmacodynamic changes. Firstly, in these patients there is an altered absorption that could be surpassed by intravenous administration [15,16]. Secondly, most patients with severe congestive heart failure have an impaired renal function which causes an accumulation of endogenous organic acids and, as a result of competition, a reduced secretion of furosemide from the proximal renal tubule with a decreased diuretic effect as a consequence [4]. As shown in our study, higher doses of furosemide enhance natriuresis by forcing sufficient amounts of furosemide into the urine.

Figure 1 *Daily urine volume and electrolyte excretions during continuous administration of furosemide (480-3840 mg 24 h^{-1}) in one representative patient. U_{Na}= urinary sodium excretion, U_K= urinary potassium excretion, U_{vol}= urinary volume, U_{creat}= urinary creatinine excretion, S_{creat}= serum creatine concentration.*



Thirdly, in patients with severe congestive heart failure there seems to be an increased sodium reabsorption from the proximal tubule as a result of kidney hypoperfusion. In addition, as shown in recent studies, diuretic could be a result of the kidney adaptation to chronic diuretic therapy, resulting in an increased NaCl reabsorption in nephron segments downstream from the site of action [11]. It seems that continuous furosemide infusion is a mode of administration that could inhibit this increased sodium reabsorption in the distal renal segment. Recently it was demonstrated in patients with renal failure, in healthy volunteers and in patients with congestive heart failure, that continuous furosemide infusion was much more efficacious than bolus administration [17-19]. Although we did not compare bolus administration with continuous infusion, it is obvious that continuous infusion of furosemide is effective. In addition, this treatment modality seems safe because the high and potentially toxic plasma concentrations seen after bolus administration would be avoided; moreover, high cumulative dosages could be administered. Toxic plasma furosemide levels were observed in one patient with the lowest ECC (13 ml. min^{-1}) who was treated with the maximum furosemide infusion rate (160 mg. h^{-1}). With respect to toxic furosemide concentrations, a daily cumulative dose of 3840 mg (infusion rate 160 mg. h^{-1}) seems safe when the ECC is higher than 23 ml. min^{-1}. As reported in the literature, loss of hearing can occur when the furosemide infusion rate is higher than 240 mg. h^{-1} [8].

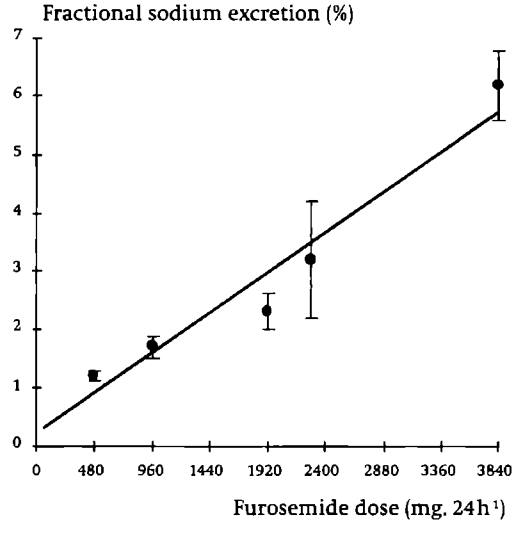


Figure 2. *Dose-response relation to continuous administration of furosemide relating the furosemide dose (mg) to fractional sodium excretion (%). Each point represents the mean (±SEM) fractional sodium excretion, calculated from the 24 h urine collections of the patients after heightening of the dose*

In all our patients this treatment was successful and well tolerated. As shown in the dose-response curve, it seems rational to give higher (cumulative) daily doses of furosemide than is generally advocated. It was not possible to fit the data according to a sigmoid E_{max} model because maximum values were not reached and consequently the full extent of the curve could not be defined [17]. An expected finding was that the responsiveness of the kidney to furosemide diminished when patients were almost compensated. As mentioned by *Vasko et al*, this could occur when patients attained dry weight and were in a sodium-avid state [15]. In addition, at that time their sodium levels were almost in balance with their diet.

During this treatment no biochemical or clinical signs of dehydration were observed. Consequently, as stated by *Anand et al*, careful clinical assessment of patients is a reliable method for preventing diuretic-induced dehydration [20]. Serum sodium normalized in most patients, as demonstrated in an earlier study in patients with severe congestive heart failure [7]. However, it must be stressed that combination with thiazides can result in severe hyponatremia because they act in the cortex and do not interfere with concentrating ability [1,22].We conclude that continuous furosemide administration is a safe, controllable and effective symptomatic treatment for patients with severe congestive heart failure and diuretic resistance. When this strategy lacks effect, combination with diuretics that exert their effect in another part of the nephron, infusion with positive inotropic drugs or hemofiltration could be helpful.

References

1 Cowley AJ, Stainer K, Wynne RD, Rowley JM, Hampton JR. Symptomatic assessment of patients with heart failure: double blind comparison of increasing doses of diuretics and captopril in moderate heart failure. Lancet 1986; 2: 770-772
2 Braunwald E, Gottlieb SN. The management of heart failure. In: Braunwald E, ed. Heart disease: a textbook of cardiovascular medicine. 3rd ed. Philadelphia: WB Saunders Co, 1988: 507-516
3 Kivinge A, Field MJ, Pawsey CC, Yiannikas J, Lawrence JR, Attel WJ. Metolazone in treatment of severe refractory congestive cardiac failure. Lancet 1990; 335: 29-31
4 Brater DC. Resistance to loop diuretics: Why it happens and what to do about it. Drugs 1985; 30: 427-443
5 Rimondini A, Cipolla CM, Della Bella P, et al. Hemofiltration as short term treatment for refractory congestive heart failure. Am J Med 1987; 83: 43-48
6 Cohn J, Franciosa JA. Selection of vasodilator, inotropic or combined therapy for the management of heart failure. Am J Med 1978; 65: 181
7 Gerlag PG, van Meijel JJ. High dose furosemide in the treatment of refractory congestive heart failure. Arch Intern Med 1988; 148: 286-291
8 Gallagher KJ, Jones JK. Furosemide-induced ototoxicity. Ann Intern Med 1979; 91: 744-745
9 Lawson DH, Gray JM, Henry DA, Tillstone WJ. Continuous infusion of frusemide in refractory oedema. Br Med J 1978; 2: 476
10 Kaojaren S, Day B, Brater DC. The time course of delivery of furosemide into urine: an independent determinant of overall response. Kidney Int 1982; 22: 69-74
11 Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 1991; 114: 886-894
12 Russel FGM, Tan Y, Meyel van JJM, Gribnau FWJ, Ginneken van CAM. Solid-phase extraction of furosemide from plasma and urine and subsequent analysis by high performance liquid chromatography. J Chromat 1989; 496: 234-241
13 de Man AJM, Hofman JA, Hendriks T, Rosmalen FMA, Benraad TJ. A direct radioimmunoassay for plasma aldosterone: significance of endogenous cortisol. Neth J Med 1980; 23: 79-83
14 Drayer JIM, Benraad TJ. The reliability of the measurement of plasma renin activity by radioimmunoassay. Clin Chim Act 1975; 61: 309-324
15 Vasko MR, Cartwright DB, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985; 102: 314-318
16 van Meijel JJ, Gerlag PG, Smits P, et al. Absorption of high dose furosemide (frusemide) in congestive heart failure. Clin Pharmacokinet 1992; 22: 308-318
17 van Meijel JJ, Smits P, Russel FG, Gerlag PG, Tan Y, Gribnau FW. Diuretic efficiency of furosemide during continuous administration versus bolus injection in healthy volunteers. Clin Pharmacol Ther 1992; 51: 440-444
18 Rudy DW, Voelker JR, Greene PK, Esparza FA, Brater DC. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. Ann Intern Med 1991; 115: 360-366
19 Lahav M, Regev A, Ra anani P, Theodor E. Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure. Chest 1992; 102: 725-731
20 Anand IS, Veall N, Kalra GS, Ferrari R, Sutton G, Tipkins D. Treatment of heart failure with diuretics, body compartments, renal function and plasma hormones. Eur Heart J 1989; 10: 445-450
21 Rose BD. McGraw-Hill ed. Clinical Physiology of acid-base and electrolyte disorders. 3rd ed. New York: McGraw-Hill, 1989
22 Szatalowicz VL, Miller PD, Jacher JW, Gordon JA, Schrier RW. Comparative effect of diuretics on renal water excretion in hyponatraemic oedematous disorders. Clin Sci 1982; 62: 235-238

DIURETIC EFFICACY OF HIGH DOSE FUROSEMIDE IN SEVERE HEART FAILURE: BOLUS INJECTION VERSUS CONTINUOUS INFUSION

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Abstract

Objectives The efficacy of high dose furosemide as a continuous infusion was compared with a bolus injection of equal dose in patients with severe heart failure

Background The delivery rate of furosemide into the nephron has been proved to be a determinant of diuretic efficacy in healthy volunteers

Methods: In a randomized crossover study we compared the efficacy of a continuous infusion of high dose furosemide (mean daily dosage 690 mg, range 250 - 2000 mg) versus a single bolus injection of an equal dose in 20 patients with severe heart failure The patients received an equal dosage, either as a single intravenous bolus injection or as an 8 h continuous infusion preceded by a loading dose (20% of total dosage)

Results Mean (±SEM) daily urinary volume infusion 2860 ±240 ml, bolus 2260 ±150 ml, p= 0 0005) and sodium excretion (infusion 210 ±40 mmol, bolus 150 ±20 mmol, p= 0 0045) were significantly higher after treatment with continuous infusion than with bolus injection, despite significantly lower urinary furosemide excretion (infusion 310 ±60 mg 24 h', bolus 330 ±60 mg 24 h', p = 0 0195) The maximal plasma furosemide concentration was significantly higher after bolus injection than during continuous infusion (infusion 24 ±5 μg ml , bolus 95 ±20 μg ml', p < 0 0001) Short term completely reversible hearing loss was only reported after bolus injection in 5 patients

Conclusions We conclude that in patients with severe heart failure, high dose furosemide administered as a continuous infusion is more efficacious than bolus injection and causes less ototoxic side effects

Introduction

Loop diuretics are commonly required in the management of heart failure In most patients orally administered conventional dosages of furosemide mobilize oedema and maintain adequate hydration However, with progression of the disease state, diuretic resistance - a potentially life-threatening phenomenon - frequently occurs, resulting in fluid and sodium retention To overcome this complication the oral dosage of the loop diuretic is often increased There are two reasons for this strategy, firstly, in the course of heart failure impairment of renal function often occurs [1] In renal insufficiency, higher dosages of furosemide are necessary to create effective concentrations in the intraluminal site of the ascending limb of Henle's loop, the site of action of loop diuretic drugs Secondly, in patients with heart failure higher concentrations of furosemide in the renal tubule are required to induce an adequate natriuretic response, in other words in these patients the dose-response curve is shifted to the right and downward [2] In addition to the absolute amount of drug carried to the site of action, the time course of delivery to the site of action appears to be an important determinant of overall diuretic response [3,4] This means that, theoretically, diuretic treatment can be optimized by the administration of furosemide as a continuous intravenous infusion This mode of administration provides a constant delivery rate of furosemide to the renal tubule Furthermore sodium retention during the drug-free intervals may be avoided and the risk for ototoxic side effects is reduced [5,6] Only two controlled studies have compared the efficacy of a continuous intravenous infusion of a loop diuretic drug with intravenous bolus administration in patients with heart failure [7,8], with conflicting results with respect to the supposed superior efficacy of continuous infusion However, on the basis of the previous arguments and the results of studies in healthy volunteers and patients with renal insufficiency, optimizing furosemide delivery to the renal tubule may have a beneficial effect Consequently, we hypothesized that high dose furosemide administered as a continuous intravenous infusion would be more efficacious and less toxic than an intravenous bolus of an equal dosage furosemide in patients with severe chronic heart failure

Patient No.	Age (yr)/ gender	Weight (kg)	Weight Change (kg)	Creatinine Clearence (ml. min^{-1})	Hydration Status	Diagnosis	Dose (mg)	Additional medication
1	74/M	70.1	0.0	46	Comp	CAD	500	A,C
2	74/M	106.9	-1.6	92	Comp	CP	1000	Al,P,T.Th
3	73/F	78.5	-0.3	70	Comp	CAD	250	A.T,N,P
4	83/F	83 9	-1.2	59	Comp	CAD	250	A,C,D,I,T
5	56/M	90.4	+1.2	87	Comp	CM	500	A,Am,C,P
6	76/M	57.2	-1.3	27	Comp	CAD	500	Al,I,Ib,Th
7	73/F	83.0	-1.6	16	Comp	CAD	500	A,Am,I.P,T
8	72/M	48.3	-0.5	15	Comp	CAD	1.500	A,Am,I
9	51/F	36.6	-0.5	15	Comp	CAD	2.000	A,I,Ib,Ac
10	82/M	61.2	-2.7	43	Decomp	CAD	500	D,T,Tr
11	71/M	81,9	-6.6	50	Decomp	CM	250	Ac,Am,C,D,I,Pr,T,Th
12	85/M	72.4	-12.8	32	Decomp	CAD	250	C,D,Ac
13	86/F	56.3	-3.8	34	Decomp	CAD	500	AI,C
14	89/F	63.6	-0.9	32	Decomp	CAD	1000	D,Ib
15	69/F	76,5	-1.0	52	Decomp	CP	250	A,C,H,Th
16	66/M	78.0	-0.5	50	Decomp	CAD	500	Am,C.P,T
17	66/M	71.0	-1.3	57	Decomp	CM	2000	A,AII,C,D,Th
18	57/M	79.7	-2.7	46	Decomp	VD	250	C,D,P
19	69/M	63.6	-1.8	24	Decomp	CAD	1000	C,T
20	51/M	98.2	-4.4	45	Decomp	CAD	250	AI,D
Mean	71	72.9	-2.3	45			690	
SEM	2.5	3.7	-0.7	4 8			120	

Table 1 *Clinical characterstics of 20 study patients*

Abbrevıations A=amılorıde, Ac=acenocoumarol, Al=aldactone, All=allopurinol, Am=amıodarone, C=captopril, CAD=coronary artery disease, CM=cardıomyopathy, Comp=compensated heart failure, CP=cor pulmonale, D=digoxin, Decomp=decompensated heart failure; F= female, H=hydroclorothıazide, I=ısosorbıdedinitrate, Ib=ıbopamine, M= male, N=nifedipine, P=potassium, Pr=prednisone, Pt=patient, T=tolbutamide, Th=theophylline, Tr=triamterene, VD=valvular disease

Subjects

After approval by the local ethics committee, we included 20 patients (7 women, 13 men) with severe heart failure of differing etiologies (New York Heart Association functional class III or IV) and long-term use of orally administered high dose furosemide (at least 250 mg) Each patient provided written informed consent before the start of the study No patient was taking non-steroidal anti-inflammatory drugs or probenecid Patients with cardiomyopathy due to alcoholism were excluded

At the time of the study, 9 patients were in a clinically compensated state without oedema and 11 patients had decompensated heart failure with an estimated oedematous mass of at least 5 kg Mean (±SEM) body weight at the start of the study was 72 9 ±3 7 kg Mean pretreatment endogenous creatinine clearance was 45 ±4 ml min The clinical characteristics of the study patients are shown in Table 1

Study design

The study was a randomized crossover study All patients were placed on a standard diet with a daily content of 80 mmol of sodium and 100 mmol of potassium and a fluid intake of 1500 ml Extra potassium was administered for hypokalemia (<3 5 mmol l^{-1}) During the study patients did not drink any coffee, tea or alcohol The daily furosemide dosage was left unchanged throughout the study All other medication was continued as previously prescribed Patients underwent physical examination with emphasis on hydration status Standing and supine blood pressures and weight were determined daily An indwelling urinary catheter was inserted when patients could not void on request The patients remained in the hospital for the duration of the study

During days 1 and 2 of the study, the patients received a single dose of orally administered furosemide (Lasix, Hoechst) At that time, blood samples were obtained for baseline measurement of serum electrolytes, blood cell counts, serum albumin, plasma epinephrine and norepinephrine, plasma renin and plasma aldosterone Urine samples were collected over 24 h for measurement of volume and concentrations of creatinine, sodium, potassium, chloride and furosemide

Table 2 *Mean values (±SEM) of biochemical variables in 20 patients with severe heart failure before and after intravenous treatment with high dose furosemide (daily dosage 690 ±560 mg)*

	Day 2	Days 3-5				Day 6
		Before Infusion (t= 0 h)	After Infusion (t= 24 h)	Before Bolus (t= 0 h)	After Bolus (t= 24 h)	
Serum sodium (mmol l^{-1})		137±1	137 ± 1	138 ± 1	138 ± 1	
Serum potassium (mmol l^{-1})		4 2 ± 0 1	4.3 ± 0 2	4 1 ± 0 1	4 3 ± 0 1	
Serum chloride (mmol l^{-1})		95 ± 1	94 ± 2	95 ± 1	94 ± 2	
Serum creatinine (μmol l^{-1})		132 ± 8	139 ± 9*	134 ± 8	139 ± 8†	
Serum urea (mmol l^{-1})		18 ± 2	19 ± 2	19 ± 2	19 ± 2	
Serum albumin (g l^{-1})		36 ± 1	37 ± 1	36 ± 1	36 ± 1	
Aldosterone (nmol l^{-1})	1 5 ± 0 2					1 8 ± 0 5
Renin (ng l^{-1})	222 ± 62					336 ± 109
Epinephrine (nmol l^{-1})	0 4 ± 0 1					0.3 ± 0 1
Norepinephrine (nmol l^{-1})	3 5 ± 0 5					2 8 ± 0 4

$p<0.01$, †$p<0.05$ versus before treatment (Student t test for paired data) t=time

On day 3, patients were randomized to receive furosemide either as an intravenous bolus injection (injected within 5 minutes) or as a continuous intravenous infusion. The continuous intravenous infusion started with a loading dose, consisting of 20% of the total dose and administered within 5 min as a bolus injection, followed by an 8 h continuous intravenous infusion at an infusion rate of 10% of the total dose per hour (model STC-521 infusion pump, Terumo Corp., Tokyo, Japan). Either of the administration modes was started at 8 AM, after initial bladder emptying. Blood samples were taken from the antecubital vein in the arm contralateral to the drug infusion at 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480 and 1440 min after the start of the intravenous furosemide administration for determination of plasma furosemide concentrations. Urine was collected at 30, 60, 120, 180, 240, 360, 420, 480 and 1440 min after the start of furosemide administration for measurements of volume, sodium, potassium, chloride, creatinine and furosemide. Intravenous furosemide preparations as well as all urine samples were protected against light to prevent photochemical degradation of furosemide. Urine losses were not replaced isovolumetrically. Day 4 was used as a washout period; patients received oral furosemide medication and blood and urine sampling was identical to the first 2 days. On day 5 the crossover mode of intravenous administration was given as described previously. On the final day (day 6), urine was collected, and blood samples (including renin, aldosterone and catecholamines) were taken for comparison with base line parameters.

Analytical methods

Sodium and potassium concentrations were measured by flame photometry, chloride concentrations by using a semiautomatic colometric titration method and creatinine concentrations according to the Jaffe reaction in an autoanalyzer. Plasma and urine concentrations of furosemide were measured by a rapid and sensitive high performance liquid chromatography assay, as described previously [9]. Plasma aldosterone was determined by radioimmunoassay [10]. Plasma renin was measured by means of an immunoradiometric sandwich technique with the use of two monoclonal antibodies and without enzymatic step (ERIA Diagnostics Pasteur, Marnes La Coquette, France) [11]. Blood samples for measurement of plasma catecholamines were collected in prechilled tubes on melting ice containing glutathione (0.2 mol l^{-1}) and EDTA (0.25 mol l^{-1}). The tubes were centrifuged at 4°C and plasma was stored at -80°C. Analyses of plasma samples and infusate occurred within 2 months from collection. Plasma samples were analyzed for concentrations of catecholamines by high performance liquid chromatography with fluorometric detection after precolumn derivatization with the selective detection agent 1,2-diphenylethylenediamine. The laboratory procedure is a modification of a previously described method [12].

Data analysis

The plasma concentration data obtained after bolus injection were fitted to an open two-compartment model by use of the PCNonlin computer program [13]. The area under the curve (AUC) was calculated by direct integration, and the half-life of furosemide was obtained from the terminal elimination rate constant. The AUC below the plasma concentration-time curve during continuous infusion was calculated by means of the trapezoid rule and extrapolation to infinity using the terminal elimination rate constant of the curve after bolus injection. Systemic clearance was determined by dividing the furosemide dose by the AUC. Renal clearance was calculated as the amount of excreted drug during 24 h divided by the AUC. Nonrenal clearance was defined as the systemic clearance minus renal clearance. Overall efficiency was calculated by dividing the excreted amount of sodium (mmol 24 h^{-1}) by the excreted amount of furosemide (mg 24 h^{-1}).

Statistical analysis

Statistical analyses of unpaired and paired data were made using the Student *t* test and the Student *t* test for paired data, respectively A *p* value < 0 05 was considered significant Data are expressed as mean value ±SEM

RESULTS

Biochemical measurements

Mean values of the biochemical parameters including catecholamines, renin and aldosterone did not change significantly during the study, with the exception of serum creatinine, which showed a significant increase after both treatment modes (Table 2) As shown in Table 1, the endogenous creatinine clearance was reduced in the majority of the patients According to the natriuresis, 13 patients were not resistant to oral therapy (Table 3) However, six of these patients had a clearly negative sodium balance (>20 mmol 24 h^{-1}) and did not lose weight during this phase of the study, suggesting poor compliance with the dietary restrictions An influence of cotreatment with angiotensin-converting enzyme inhibitors on the diuretic response could not be observed The renin levels between captopril-treated and non captopril treated patients did not differ significantly

Table 3 *Urinary volume electrolyte and furosemide excretion (mean ±SEM) 8 and 24 h after administration of furosemide as oral dosage (day 2), intravenous bolus injection or continuous infusion in patients with heart failure*

		Bolus		Infusion		Bolus versus Infusion (*p* value)	
	Oral, 0-24 h	0-8 h	0-24 h	0-8 h	0-24 h	0-8 h	0-24 h
U_v (ml)	2200 ±160	1350 ±90	2260 ±150	1700 ±120	2860 ±240	0 0002	0 0005
U_{Na} (mmol)	130 ±30	110 ±10	150 ±20	140 ±20	210 ±40	0 0010	0 0045
U_k (mmol)	70 ± 6	30 ±5	70 ±5	40 ±4	80 ±5	0 0006	<0 0001
U_{Cl} (mmol)	130 ±20	120 ±10	150 ±20	150 ±20	220 ±35	0 0006	0 0018
$U_{furosemide}$ (mg)	140 ±30	290 ±50	330 ±60	220 ±40	310 ±60	<0 0001	0 0195
Recovery (%)	21 ±2	44 ±2	50 ±2	33 ±2	44 ±2	<0 0001	0 0195
Eff (mmol mg^{-1})	2 9 ±1 5	0 7 ±0 2	0 9 ±0 3	1 1 ±0 3	1 3 ±0 4	0 0005	0 0019

Abbreviations Eff = efficiency, U_v = urinary volume, U_{Na} = urinary sodium excretion, U_k = urinary potassium excretion, U_{Cl} = urinary chloride excretion
Statistical analyses were made using the Student t test for paired data

Pharmacokinetic parameters

Apart from the maximal plasma furosemide concentration, which was significantly higher after intravenous bolus injection, the pharmacokinetic measurements were similar in the two treatment modes (Table 4)

Table 4 *Pharmacokinetic variables (mean +SEM) of furosemide after administration as bolus or continuous infusion in 20 patients with heart failure*

	Bolus	Infusion
AUC (g ml^{-1} min^{-1})	14 2 ±4 0	13 1 ±4 1
Systemic clearance (ml min^{-1})	64 ±8	67 ±6
Renal Clearance (ml min^{-1})	30 ±3	31 ±3
Nonrenal clearance (ml min^{-1})	34 ±4	36 ±4
Half life (min)	139 ±7	
Furosemide excretion (mg 24 h^{-1})	330 ±60*	310 ±60

Abbreviation AUC = area under the curve

**p<0 05 statistical analyses were made using the Student t test for paired data*

The plasma furosemide concentration-time profiles of the two dose regimens of one representative patient are shown in Figure 1

The furosemide plasma concentrations were in the supposed ototoxic range (>100 μg ml^{-1}) in seven patients immediately after bolus injection and in one patient during continuous infusion During continuous infusion, the plasma furosemide concentration remained at steady state throughout the infusion period, with a significantly lower maximal plasma concentration (bolus 95 ±20 mg ml^{-1}, infusion 24 ±5 mg ml^{-1}, $p < 0\ 0001$) However, the plasma furosemide concentration was determined first at 15 min, after the start of the administration This implies that immediately after injection of the bolus, the plasma furosemide concentration was even higher The urinary furosemide excretion rate followed a similar pattern for both ways of administration (Figure 1)

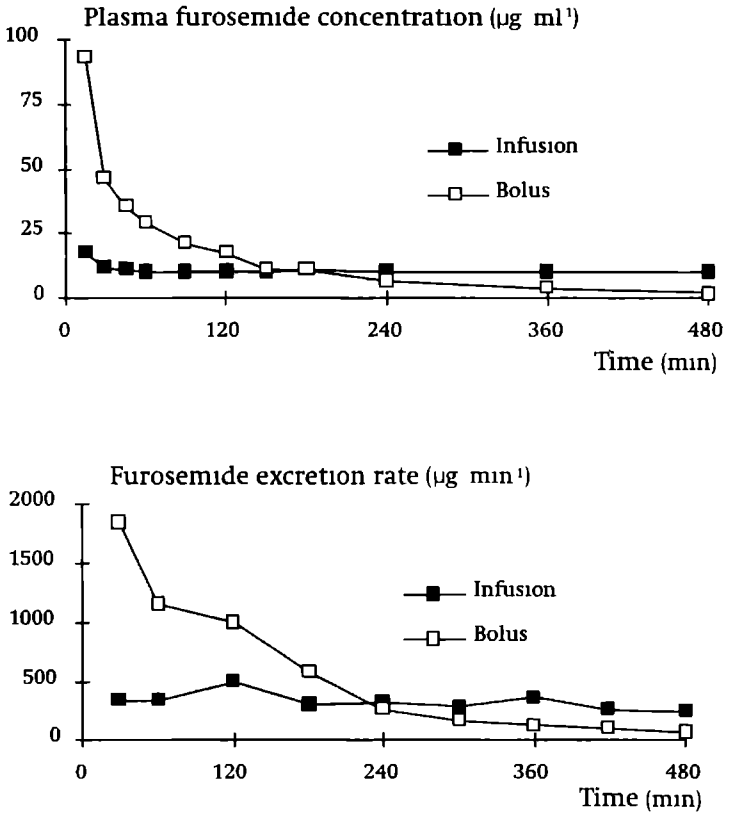

Figure 1 *Furosemide plasma concentration (Top) and urinary furosemide excretion rate (Bottom) for a representative study patient (patient 1) after 500 mg of furosemide as a bolus injection or continuous infusion (50 mg h⁻¹ during 8 h preceded by a loading dose of 100 mg)*

After bolus injection, most of the furosemide was excreted within 2 h, whereas during continuous infusion, the urinary excretion rate was constant

Pharmacodynamic parameters

Although a smaller amount of furosemide was excreted in the urine during both 8 and 24 h with the use of continuous infusion, the urinary volume and natriuresis during both 8 and 24 h were significantly larger (Table 3) The differences in natriuretic response between the two intravenous modes of administration and the interindividual variability of these responses are shown in Figure 2 and 3

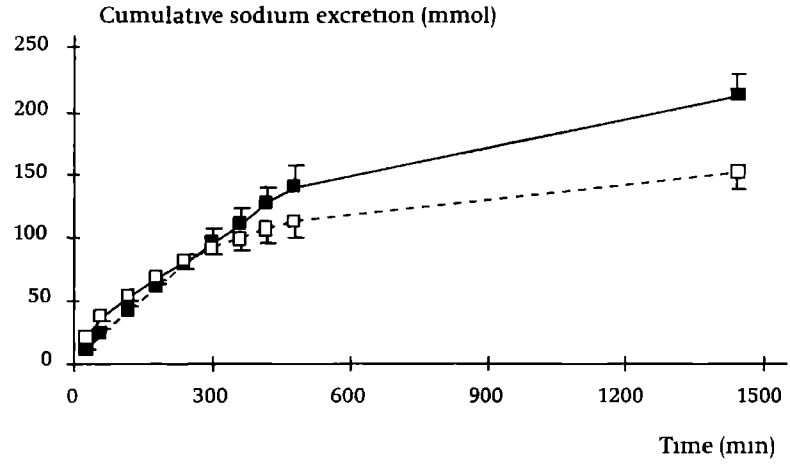

Figure 2 *Cumulative urinary sodium excretion (mean ±SEM) 24 h after bolus injection (open squares) and continuous infusion (solid squares) of high dose furosemide*

Separate analysis of data of patients with compensated (n=9) and decompensated (n=11) heart failure revealed similar results for these subgroups, except for the urinary furosemide excretion In the two dose regimens there appeared to be a significantly lower excretion only in patients with compensated heart failure after continuous infusion The sequence of drug administration did not influence the natriuretic response in either of the two intravenous administration methods Compared with oral therapy (day 2) bolus injection did not differ significantly with respect to volume and electrolyte excretion However, urinary recovery of furosemide was significantly lower (oral 21 ±2%, bolus 50 ±2 % $p<0.0001$), and thus efficiency higher When continuous infusion was compared with oral therapy, volume and electrolyte excretion was significantly higher after continuous infusion, whereas urinary furosemide recovery was significantly lower after oral administration (oral 21 ±2 % infusion 44 ±2%, $p<0.0001$)

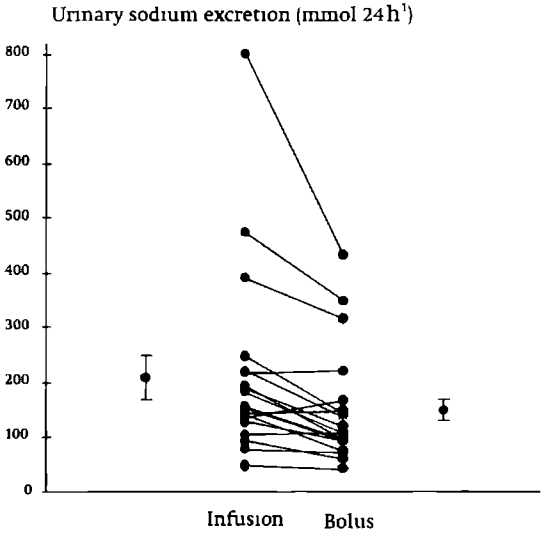

Figure 3 *Individual values for urinary sodium excretion 24 h after continuous infusion and bolus injection of high dose furosemide in 20 patients with severe heart failure*

A dose-response curve was created for each patient However, sigmoid-shaped curves as seen in healthy subjects, were not observed (data not shown) Moreover, a high interindividual variability was observed To gain insight into the potential development of acute diuretic tolerance during continuous infusion of furosemide we compared the efficiency (mmol excreted sodium divided by mg of excreted furosemide) during two time intervals- 30-60 min and 420-480 min The amount of drug excreted per hour during each interval did not differ significantly, nor did the amount of sodium Hence, the efficiency was equal in both periods indicating that acute diuretic tolerance did not occur during continuous infusion Because of the design of the study (a single bolus instead of multiple) we could not determine whether acute drug tolerance was present after bolus injection

Side effects

Although five patients reported hearing loss or tinnitus,or both, shortly after bolus injection this appeared to be transient in all five and disappeared within 15 min No other side effects were observed or reported during this study

Discussion

General conclusions

Our results clearly show that in patients with severe heart failure, continuous infusion of high dose furosemide causes excretion of a higher volume of urine and electrolytes than an equal dose administered as an intravenous bolus, and the maximal plasma furosemide concentration is significantly lower A crossover design in combination with a washout period was used to balance out any possible time or sequence trends Moreover, the pharmacokinetic data obtained supported the outcome of the study

Comparison with previous studies

Few data are available on the usefulness of continuous infusion of furosemide in disease, particularly in heart failure In an animal study, *Lee et al* [14] compared different durations of infusion of an equal dosage of furosemide The diuretic response increased with increasing infusion times In healthy volunteers a controlled comparison of bolus injection with continuous infusion of a conventional dosage of furosemide showed a larger diuretic effect of the latter mode of administration [4] In chronic renal insufficiency continuous infusion of bumetanide was more effective and less toxic than intermittent bolus therapy [15] Several uncontrolled reports describing small series of patients with congestive heart failure demonstrate succesful application of continuous infusion of loop diuretic drugs [5,16 20]

To our knowledge only two controlled studies on this subject have been performed in patients with heart failure [7,8] *Copeland et al* [8] did not find any significant pharmacodynamic differences in a comparison of continuous intravenous infusion and an equal dose given as two separate bolus injections in patients after cardiac surgery However, that study lacked a crossover design, use of a loading dose before the start of continuous infusion and adequate study period *Lahav et al* [7] compared intermittent administration of furosemide with a continuous infusion of an equal dose in patients with congestive heart failure In their study which lacked pharmacokinetic data, continuous infusion was shown to be the preferred method of administration In both studies conventional dosages of furosemide were used

In our study the dosage of furosemide was ≥ 250 mg day^{-1} in all patients The results of the present study can not be generalized to patients receiving furosemide in the conventional dose range However, in the conventional dose range a continuous infusions is usually not necessary, because diuretic resistance can be overcome by simply increasing the dosage

Interpretation of pharmacokinetic and pharmacodynamic data

In the present study, we included those patients who would benefit most from the presumed advantages of continuous infusion of furosemide, that is, patients with heart failure and, often impairment of renal function. High dose furosemide is used in these patients because of diuretic resistance to conventional dosages. Thus, they are in need of an optimal diuretic regime without toxic side effects. The higher efficiency of continuous infusion is demonstrated by the observation that a smaller amount of drug excreted into the urine produced a larger natriuretic effect (Table 3). Several mechanisms may elicit this superior response: firstly the time course of delivery of furosemide into urine. Because the amount of drug excreted into the urine is even smaller after continuous infusion, the time course of delivery is consequently an important factor influencing the diuretic response. The maximally efficient excretion rate of furosemide can be calculated and the slope factor of the dose-response curve appears to be an important determinant in this calculation [3,4]. In healthy volunteers the maximally efficient excretion rate appeared to be 115 μg/min [4]. As in patients with heart failure studied by *Brater et al*, the dose-response curves of the patients in the present study were shifted to the right [2]. Moreover, the sigmoid shape could not be recognized, making a calculation of the maximally efficient excretion rate impossible. For this reason and because of the larger interindividual variability, an optimal infusion rate of furosemide can not be predicted in these patients. However it is obvious that during continuous infusion, the urinary furosemide excretion rate will be closer to the maximally efficient excretion rate over a longer period.

Another cause for the observed difference in response between the two modes of administration could be the development of a more pronounced acute drug tolerance after bolus injection [21]. Because of a greater diuresis during the period immediately after the injection, the intravascular volume might decrease even in a volume-overloaded patient, causing activation of sodium- and volume retaining mechanisms. The net result may be a smaller diuretic efficacy despite adequate urinary furosemide concentrations. Because we used only one bolus injection instead of multiple intermittent injections, the presence of acute tolerance could not be verified. Acute diuretic tolerance during continuous infusion appeared to be absent.

Finally, after bolus injection the drug free interval during which counteracting sodium retaining mechanisms are active, is longer. Although catecholamine levels were increased at the start of the study they were not increased further at the end of the study. Activation of the renin angiotensin aldosterone axis was not observed (Table 2). However variables were measured at the start and at the end of the study, so a transient activation could have been missed. In chronic heart failure long-term coadministration of angiotensin-converting enzyme inhibitors may enhance furosemide induced natriuresis, possibly owing to a change in the set point for renal sodium handling [22]. In 9 out of 20 patients in this study, angiotensin-converting enzyme inhibitors were withdrawn in an earlier phase, because of further deterioration of renal function or symptomatic hypotension. Comparison of the patients treated with and without angiotensin-converting enzyme inhibitors did not reveal any differences in furosemide-induced natriuresis for any of the modes of administration, and the mean daily dosage of furosemide did not differ significantly between the two groups.

Side effects

An important advantage of the use of continuous infusion is a smaller risk of ototoxicity, because high peak plasma levels of furosemide are avoided [6] In the present study the measured maximal plasma concentration during continuous infusion was lower than after bolus injection in all patients However, even a continuous infusion of high dose furosemide may lead to concentrations in the supposed ototoxic range in patients with severe renal insufficiency, as illustrated by one of the study patients (patient 9, endogenous creatinine clearance 15 ml min^{-1} 1 73 m^{-2}, furosemide dosage 2000 mg, maximal plasma concentration in the course of continuous infusion 119 μg ml) According to our clinical experience an infusion rate of 160 mg h^{-1} seems safe, when the endogenous creatinine clearance is higher than 20 ml min^{-1} 1 73 m [5]

Intravenous versus oral treatment

We observed a higher urinary recovery of furosemide after bolus injection than with continuous infusion This difference reached significance only in the compensated group of patients The exact mechanism of this discrepancy is not clear and needs further exploration Although the urinary recovery of furosemide after oral therapy is much lower (Table 3), owing to a lower bioavailability than after bolus injection, its efficacy is equal This means that the efficiency is higher after oral therapy than after bolus injection, which is probably the result of a better time course of delivery Although efficiency was equal in oral therapy and continuous infusion, the continuous infusion of an equal dose is more efficacious than oral administration because of a higher urinary excretion rate of furosemide with continuous infusion (Table 3) In patients with congestive heart failure, absorption of furosemide after oral therapy is delayed which results in lower drug concentration at the site of action An increase of oral dosage is less attractive, because the exact duration of delay is unknown, making the response unpredictable For this reason patients with manifest decompensated heart failure should preferably be treated with intravenous therapy, until the hydration state is corrected

Summary

The value of continuous infusion of furosemide in patients with severe congestive heart failure can be summarized as follows a higher efficiency (than with bolus injection) and a higher, more predictable urinary excretion rate of drug (than after oral therapy) results in an improved diuretic response combined with a reduced risk for ototoxicity Continuous infusion of furosemide should be considered in patients with decompensated heart failure whenever the diuretic response after oral therapy with high dose furosemide is insufficient, especially in those patients at risk for furosemide-induced toxicity because of impaired renal function

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References

1 Gerlag PG and van Meijel JJ high dose furosemide in the treatment of refractory congestive heart failure Arch Intern Med 1988 148 286 291
2 Brater DC Chennavasin P and Seiwell R Furosemide in patients with heart failure shift in dose response curves Clin Pharmacol Ther 1980 28 182 186
3 Kaojarern S Day B and Brater DC The time course of delivery of furosemide into urine an independent determinant of overall response Kidney Int 1982 22 69 74
4 van Meyel JJ Smits P Russel FG Gerlag PG Tan Y and Gribnau FW Diuretic efficiency of furosemide during continuous administration versus bolus injection in healthy volunteers Clin Pharmacol Ther 1992 51 440 444
5 van Meyel JJ Smits P Dormans T Gerlag PG Russel FG and Gribnau FW Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance J Intern Med 1994 235 329-334
6 Rybak LP Pathophysiology of furosemide ototoxicity J Otolaryngol 1982 11 127 133
7 Tahav M Regev A Ravanani P and Theodor E Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure Chest 1992 102 725-731
8 Copeland JG Campbell DW Plachetka JR Salomon NW and Larson DF Diuresis with continuous infusion of furosemide after cardiac surgery Am J Surg 1983 146 796 799
9 Russel FGM Tan Y Meyel van JJM Gribnau FWJ and Ginneken van CAM Solid phase extraction of furosemide from plasma and urine and subsequent analysis by high performance liquid chromatography J Chromat 1989 496 234-241
10 Man de AJM Holman JA Hendriks I Rosmalen JMA and Bernaad TJ A direct radioimmunoassay for plasma aldosterone significance of endogenous cortisol Neth J Med 1990 23 79 84
11 Simon D Hartmann DJ Badouaille G et al Two-site direct immunoassay specific for active renin Clin Chem 1992 38 1959-1962
12 Hoorn van der EAJ Boomsma F Man in t Veld AJ and Schalekamp MADH Determination of catecholamines in human plasma by high-performance liquid chromatography comparison between a new method with fluorescence detection and an established method with electrochemical detection J Chromat 1989 487 17 28
13 Metzel C M and Wentel D L PC Nonlin 3 0 software for statistical analysis of nonlinear models on micros Lexington 1989
14 Lee MG Li T and Chiou WL Effect of intravenous infusion time on the pharmacokinetics and pharmacodynamics of the same total dose of furosemide Biopharm Drug Dispos 1986 7 537 547
15 Rudy DW Voelker JR Greene PK Esparza FA and Brater DC Loop diuretics for chronic renal insufficiency a continuous infusion is more efficacious than bolus therapy Ann Intern Med 1991 115 360 366
16 Gray JM Henry DA Lawson DH Tilstone WJ and Longman HJ Continuous infusion of frusemide in refractory oedema Br J Pharmacol 1978 64 453P
17 Lawson DH Gray JM Henry DA and Tillstone WJ Continuous infusion of frusemide in refractory oedema Br Med J 1978 2 476
18 Magovern JA and Magovern GJJ Diuresis in hemodynamically compromised patients continuous furosemide infusion Ann Thorac Surg 1990 50 482 484
19 Singh NC Kissoon N al Mofada S Bennett M and Bohn DJ Comparison of continuous versus intermittent furosemide administration in postoperative pediatric cardiac patients Crit Care Med 1992 20 17 21
20 Krasna MJ Scott GL Scholz PM Spotnitz AJ Mackenzie JW and Penn I Postoperative enhancement of urinary output in patients with acute renal failure using continuous furosemide therapy Chest 1986 89 294 295
21 Hammarlund MM Odlind B and Paalzow LK Acute tolerance to furosemide diuresis in humans Pharmacokinetic pharmacodynamic modeling J Pharmacol Exp Ther 1985 233 447 453
22 Good JM Brady AJ Noormohamed FH Oakley CM and Cleland JG Effect of intense angiotensin II suppression on the diuretic response to furosemide during chronic ACI inhibition Circulation 1994 90 220 224

CHRONIC INTERMITTENT HEMOFILTRATION AND HEMODIALYSIS IN END STAGE CHRONIC HEART FAILURE WITH OEDEMA REFRACTORY TO HIGH DOSE FUROSEMIDE

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Abstract

Objective: To assess the benefits and problems of chronic intermittent treatment with hemofiltration or hemodialysis or both in patients with severe chronic heart failure (New York Heart Association class III or IV) and oedema refractory to pharmacological treatment

Design and setting: A retrospective case-cohort study A general hospital in The Netherlands

Patients: The results of chronic intermittent treatment with hemofiltration (n=10) and hemodialysis (n=2) were analyzed in patients with severe chronic heart failure, predominantly due to coronary heart disease and oedema refractory to a pharmacological regime including high dose furosemide

Intervention: Patients had an average (±SD) of 25 ±38 treatments

Results: There was improvement of NYHA class IV to III in seven patients However, this was not reflected in a decrease of hospital admission only two patients could be managed as outpatients The median survival after start of the treatment was 24 days (varying from 0 to 393 days) In four patients the treatment was discontinued after discussion with the patient and family

Conclusion: The use of chronic intermittent hemofiltration and hemodialysis is of limited value in end stage chronic heart failure with oedema, refractory to maximal conventional treatment

INTRODUCTION

Chronic heart failure is a major health problem Ultimately many patients become unresponsive to maximal conventional treatment and remain severely symptomatic Short term relief of symptoms may be obtained by removing fluid either by venesection, hemodialysis hemofiltration, or peritoneal dialysis [2,3,4,5,6,7] The use of these techniques in the acute setting may be worthwhile and can result in the restoration of diuretic responsiveness

Chronic intermittent hemofiltration and continuous ambulatory peritoneal dialysis of patients with heart failure may improve survival [8,9,10,11] The wide range in outcome in these studies reflects the differing definitions of maximal pharmacological treatment and the heterogeneity of the patients studied Often data are lacking about the maximal dosages of diuretics, the use of inotropic or preload reducing drugs, and the severity of left ventricular dysfunction at the start of chronic intermittent treatment We therefore set out to determine whether hemofiltration and hemodialysis used in this way can improve the quality of life in patients with chronic heart failure unresponsive to maximum conventional treatment, including high dosages furosemide (500 to 4000 mg daily dosage)

METHODS

Patient characteristics

In this retrospective study we reviewed the data of 12 patients who were treated in our hospital between October 1979 and April 1991 The clinical characteristics of the studied patients are shown in Table I The mean age of the studied patients was 68 years, the predominant cause of chronic heart failure was coronary heart disease, and all but one were in New York Heart Association (NYHA) class IV Other complicating conditions were also commonly present other vascular diseases (n=7), diabetes mellitus (n=4), chronic obstructive pulmonary disease (n=1) and renal disease (n=4) All patients were severely symptomatic with marked peripheral oedema Left ventricular ejection fraction values, by cross sectional echocardiography, were 21-30% (n=2), 11-20% (n=3) and less than 10% (n=4) The resting supine systolic blood pressure ranged from 130 to 60 mm Hg (median 90 mm Hg)

Table 1 *Characteristics of the patients before the start of the hemofiltration treatments*

Patient	Sex	Age (years)	NYHA	Underlying Disease	Furosemide Dosage (mg)	Other medication
1	M	64	IV	CHD	500 PO	Dig Vd
2	F	75	IV	CHD	1000 PO	Dig
3	M	62	IV	CM	1500 PO	Dig Ace
4	M	77	IV	CHD	1000 PO	Dig Ace, Vd Do
5	M	71	IV	CHD	2000 IV	Dig, Ace
6	M	76	IV	CHD	1500 PO	Dig Ace Vd
7	M	61	III	CHD	2000 IV	Dig Ace
8	F	71	IV	VAD	2000 PO	Dig Ace Do
9	M	56	IV	CHD	1000 PO	Ace
10	M	72	IV	CHD	2000 PO	Ace Do
11	M	66	IV	CHD	4000 IV	Ace Do
12	M	64	IV	CHD	3000 IV	Dig Ace Do

Abbreviations Ace = angiotensin converting enzyme inhibitor, CHD = coronary heart disease, CM = cardiomyopathy, Dig = digitalis, Do = dopamin, F = female, IV = intravenously, M = male PO = orally, Pt = patient, VAD = valvular disease, Vd = vasodilator

Previous treatment

Treatment consisted of salt restriction bed rest and drug treatment including diuretics ACE inhibitors digoxin and dopamine (Table 1) All patients showed diuretic resistance defined as a failure to lose weight or to develop a negative sodium balance despite bedrest a sodium intake restriction of 80 mmol per day and high dose furosemide (1790 ±960 mg) Furosemide was given orally in eight patients and by continuous intravenous infusion in four Doses of furosemide exceeding 250 mg per day were given for at least 22 days (mean 236 ±209 days) before the start of hemofiltration or hemodialysis

Laboratory data at the start

Before hemofiltration renal function was considerably decreased in all patients Endogenous creatinine clearance (ECC) ranged from 8 to 26 ml min 1 73 m with a mean ECC of 15 7 + ±6 4) ml min 1 73 m The mean urea concentration was 40 4 ±13 6 mmol l' (ranging from 20 3 to 68 0 mmol l) The serum sodium concentration varied from 118 to 146 mmol l mean 132 ±7 1 mmol l' Serum potassium before treatment varied from 3 2 to 6 1 mmol l mean 4 5 ±1 0 mmol l The mean hemoglobulin concentration was 7 8 ±1 1 mmol l (range 6 0 to 9 9 mmol l)

RESULTS

Hemodialysis and hemofiltration

The initial treatment consisted of hemofiltration (n=10) or hemodialysis (n=2) During the first session a double lumen femoral vein catheter was used as a vascular access in seven patients a subclavian double lumen catheter in one a Scribner shunt in one and a Cimino-Brescia fistula in three

The mean number of hemodialysis or hemofiltration treatments per patient was 25 ±38 (ranging from one to 113) The mean treatment interval was 5 7 ±9 1 days (Table 2) The maximum treatment interval was 33 days The mean weight reduction during the first treatment procedure was 4 0 ±1 7 kg (ranging from 1 2 to 6 2 kg) The total weight reduction (weight before first treatment minus weight before last treatment) was 8 4 +8 5 kg (Table 2)

Complications, quality of life, survival

Four patients reported no complaints during the treatment, one reported nausea and loss of hearing as main complaints while three suffered from angina pectoris unresponsive to pharmacological treatment Four patients became confused or had a decreased level of consciousness Seven improved from NYHA class IV to class III while five showed no change In four patients the treatment was discontinued after discussion with the patient or his family Other causes of death were hypotension (three patients) respiratory insufficiency (two patients) and sudden death probably caused by a fatal arrhytmia (three patients)

Patients were admitted to hospital for 12 ±9 % of the time during treatment with high dose furosemide During the treatment with hemofiltration or hemodialysis patients were in hospital for 80 ±35 4 % of the time Eight patients were in hospital continuously two were managed as outpatients for the major part of their treatment while two were discharged for a short period (14 (of 24) and 23 (of 393) days respectively)

Table 2 *Clinical data concerning the hemofiltration treatment*

Patient	Method	Mean treatment interval (days)	Total weight reduction (kg)	NYHA class during treatment	Period of treatment (days)	Cause of death
1	HD	2 3	6 8	III	233	DT
2	HF	1 9	15 1	III	21	RI
3	HF	33 0	7 4	III	165	CS
4	HF	3 0	9 7	IV	9	DT
5	HF	12 0	6 9	IV	24	DT
6	HF	3 0	18 7	III	24	DT
7	HD	3 5	1 5	II	393	FA
8	HF	2 2	1 6	III	20	CS
9	HF	1 7	7 9	III	22	FA
10	HF	0 0	1 2	IV	0	CS
11	HF	2 2	21 1	III	76	RI
12	HF	3 0	17 2	IV	24	FA

Abbreviations CS= cardiogenic shock, FA= fatal arrhytmia, HD= hemodialysis, HF= hemofiltration Pt= patient, RI= respiratory insufficiency, DT=discontinuation of treatment

The median survival after the start of hemofiltration treatment was 24 days, varying from 0 to 393 days The median survival after the last treatment was three days, varying from 0 to 23 days

Discussion

High dose furosemide is an effective, safe and controllable means of treating patients with severe chronic heart failure refractory to the conventional dosages of furosemide [12], but resistance even to high dose furosemide may develop Our study shows that the use of hemofiltration and hemodialysis in patients with end stage chronic heart failure, who have become unresponsive to such pharmacological treatment is of little benefit for either length or quality of life

Peritoneal dialysis and hemofiltration may be of value in the treatment of patients with acute heart failure unresponsive to high dosages of diuretics and inotropic drugs [2,3,4,5,6,7] However, the place of these nonpharmacologic approaches, used on a chronic intermittent basis in the treatment of refractory congestive heart failure remains unclear although the idea that excess of body water can be removed on a regular basis by the use of peritoneal dialysis or hemofiltration, analogous to the treatment of end stage renal failure, seems appealing

In contrast to hemodialysis, adverse hemodynamic effects are limited in peritoneal dialysis and hemofiltration, which makes these two techniques more suitable for the treatment of refractory chronic heart failure [13] Despite its negative hemodynamic side effects, two patients in this study had to be treated with hemodialysis because of life threatening uremia Renal function was seriously impaired initially in all patients, at least in part because of heart failure, and declined further during treatment with hemofiltration in the majority

In some of the studies describing the use of hemofiltration or peritoneal dialysis in chronic heart failure, an improvement in both hemodynamics and responsiveness to diuretics after the first session was observed, making further treatment of this kind unnecessary [2, 4, 5, 6, 7, 10]. This can not be completely explained by the influence of massive oedema on the pharmacokinetics and pharmacodynamics of high dose furosemide [14]. In our study only one patient could be treated at intervals of greater than 10 days over a long period.

Life was substantially prolonged in only four patients and the median survival after the start of hemofiltration was short. Moreover, most patients were in hospital throughout the period of hemodialysis. Any improvement in NYHA class was limited. The slight benefit combined with the high cost, make it questionable whether patients with end stage chronic heart failure refractory to high dose furosemide should be offered chronic hemofiltration. The addition of a thiazide diuretic, acting on the distal tubule, is effective, even in patients with a markedly impaired renal function [15]. Treatment with a combination of diuretics acting on different segments of the nephron may be an alternative to chronic intermittent hemofiltration. In our view treatment with hemofiltration or hemodialysis in patients with chronic heart failure should only be considered when a remedial cause of heart failure is suspected or as a bridge to heart transplantation [10,12].

References

1 Rodeheffer RJ Jacobsen SJ Gersch BJ Phil D Kottke TE McGinn A et al The incidence and prevalence of congestive heart failure in Rochester Minnesota Mayo Clin Proc 1993 68 1143 50
2 Rimondini A Cipolla CM Della Bella P Grazi S Sisillo E Susini G et al Hemofiltration as short term treatment for refractory congestive heart failure Am J Med 1987 83 43 8
3 Silverstein MF Ford CA Tysaght MJ Henderson LW Treatment of severe fluid overload by ultrafiltration N Engl J Med 1974 291 747 51
4 Morgan SH Mansell MA Thompson FD Fluid removal by hemofiltration in diuretic resistant cardiac failure Br Heart J 1985 54 218-9
5 Simpson IA Rae AP Simpson K Gribben J Boulton Jones JM Allison MEM et al Ultrafiltration in the management of refractory congestive heart failure Br Heart J 1986 55 344 7
6 Shilo S Slotki IN Iaina A Improved renal function folowing acute peritoneal dialysis in patients with intractable congestive heart failure Isr J Med Sci 1987 23 821 4
7 Fauchald P Torlang K Amlie J An evaluation of ultrafiltration as treatment of therapy resistant cardiac edema Acta Med Scand 1986 219 47 51
8 Biasoli S Barbaresi M Petrosino I Cavallini I Zambello A Cavalcanti G et al Intermittent venovenous hemofiltration as a chronic treatment for refractory and intractable heart failure ASAIO J 1992 38 M658 M663
9 McKinnie JJ Bourgeois RJ Husserl FE Long term therapy for heart failure with continuous ambulatory peritoneal dialysis Arch Intern Med 1985 145 1128 9
10 Rubin J Ball R Continuous ambulatory peritoneal dialysis as treatment of severe congestive heart failure in the face of chronic renal failure Arch Intern Med 1986 146 1533 6
11 Konig P Geissler D Iechleitner P Spielberger M Dittrich P Improved management of congestive heart failure use of continuous ambulatory peritoneal dialysis Arch Intern Med 1987 147 1031 4
12 Gerlag P van Meyel J High dose furosemide in the treatment of refractory congestive heart failure Arch Intern Med 1988 148 286 91
13 Ultrafiltration and haemofiltration for refractory congestive cardiac failure [editorial] Lancet 1986 X 1193
14 van Meyel J Gerlag P Smits P Russel F Tan Y van Ginneken C et al Absorbtion of high dose furosemide in congestive heart failure Clin Pharmacokinet 1992 22 308 18
15 Dormans I Gerlag P Combination of high dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure Diuretics IV chemistry pharmacology and clinical applications Excerpta Medica 1993 Amsterdam

COMBINATION OF HIGH-DOSE FUROSEMIDE AND HYDROCHLOROTHIAZIDE IN THE TREATMENT OF REFRACTORY CONGESTIVE HEART FAILURE

Tom P.J. Dormans and Paul G.G. Gerlag

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Abstract

Objective: We studied the synergism between high dose furosemide and hydrochlorothiazide in patients with severe congestive heart failure and impaired renal function showing diuretic resistance to daily dosages furosemide of at least 250 mg

Design and setting: An open study A general hospital in The Netherlands

Methods: In 20 patients with severe congestive heart failure (stage III-IV according to the New York Heart Association) with an oedematous mass of more than 5 kg and a proven diuretic resistance to high dose furosemide, hydrochlorothiazide (25-100 mg daily) was added to the medication for 3-12 days, leaving the other medication unchanged After correction of the hydration state, hydrochlorothiazide was withdrawn Variables included body weight, serum electrolytes, renal function and natriuresis

Results: Addition of hydrochlorothiazide resulted in a mean (±SD) body weight reduction of 6 7 ±3 3 kg per patient Mean daily urine volume increased from 1899 ±958 ml to 3065 ±925 ml ($p < 0$ 001) Fractional sodium excretion increased significantly from 3 5 ±3 2 % to 11 5 ±9 0 % ($p < 0$ 001) The most important side effect of this combination therapy appeared to be hypokalemia Mean endogenous creatinine clearance decreased (not significantly) from 32 7 ±22 5 ml min^{-1} 1 73 m^{-2} to 27 6 ±22 5 ml min^{-1} 1 73 m

Conclusions: Addition of hydrochlorothiazide to high dose furosemide is a powerful diuretic tool, even in patients with an importantly reduced renal function Because of its potentially dangerous side effects (hypokalemia), it should be used in a carefully controlled setting

INTRODUCTION

In the majority of patients with congestive heart failure no causal treatment for the underlying disease is available, thus only symptomatic therapy remains The basis of the management of decompensated patients consists of restriction of both physical activity and sodium intake together with pharmocological therapy In the management of patients with advanced chronic heart failure, pharmacological treatment comprises angiotensin converting enzyme inhibitors, vasodilators, digitalis and diuretics [1] Diuretics, most frequently the potent loop diuretics, are universally used once fluid retention occurs

The usually recommended doses of loop diuretics will lead to clinical improvement in the majority of the patients, but in some this fails to reduce oedema In patients with refractory congestive heart failure glomerular filtration rate is often significantly reduced to a level of about 30 ml min due to both prerenal (low cardiac output, renal vasoconstriction due to sympathetic excitation) and renal (arteriosclerosis) factors [2] In these cases, conventional doses of loop diuretic appear to be too low to create an adequate concentration of loop diuretic in the renal tubule, resulting in an insufficient diuretic response In these patients, administration of high dose furosemide (250 to 4000 mg per day) - supplied either orally or as a more effective continuous intravenous infusion- has been shown to be effective and safe [2,3] However, in a few patients with severe congestive heart failure even chronic therapy with high dose furosemide fails to reduce the volume of the extracellular compartment to the desired level and again diuretic resistance ensues A combination of diuretics acting on different segments of the nephron may then be a possible approach to master diuretic resistance

The synergism between loop diuretics and thiazides have been described in several studies [4-13] However, in all studies concerning the synergism of diuretics, loop diuretic doses were relatively low (i e oral furosemide dosages lower than 500 mg day^{-1}) and in most of these studies renal function was fair While thiazides used as monotherapy are thought to be no longer effective when the glomerular filtration rate falls below approximately 25 to 30 ml min^{-1} [14,15], there are nevertheless limited data showing that addition of a thiazide to a loop diuretic increases natriuresis in patients with advanced renal failure [10,16] We studied the effects of the addition of hydrochlorothiazide to high dose furosemide in patients with severe congestive heart failure who showed an impaired natriuretic response to high dose furosemide (250-4000 mg), or who were already receiving the drug in combination with a diuretic acting on the collecting ducts

Table 1 *Characteristics of study patients and diuretic regimes*

Patient no	Sex M/F	Age (years)	Cause of illness	Furosemide Dosage (mg day^{-1})	Other Diuretics (mg day^{-1})	HCTZ Dosage (mg day^{-1})	Period of Combination (days)
1	M	61	CM	2000 PO	TRIAM 50	100	8
2	M	71	CAD	2000 PO	SPIRO 50/AMILO 10	100	4
3	M	58	CAD	2000 PO		50	3
4	M	64	CAD	4000 IV	AMILO 10	50/100	3/7
5	M	73	CAD + VD	2000 PO	AMILO 5/TRIAM 50	100	4
6	M	66	CAD	500 PO		25/50/100	6/3/3
7	M	69	CAD	2000 PO	SPIRO 100	50	3
8	F	70	VD	500 PO	AMILO 10	50	5
9	M	86	CAD	4000 IV	TRIAM 50	100	3
10	M	78	CAD	1000 IV	TRIAM 50	25	4
11	M	83	CAD	500 PO	TRIAM 50	25	4
12	M	86	CAD	500 PO	AMILO 5	25	5
13	M	51	CM	500 PO	SPIRO 100	25	7
14	F	80	CAD	2000 IV	TRIAM 50	50	15
15	F	81	CAD	1000 PO		25	5
16	F	83	CAD	2000 IV		25	6
17	M	78	VD	2000 IV	TRIAM 50	25	9
18	M	30	CM	3000 IV	AMILO 10	25	15
19	F	79	VD	250 PO	AMILO 5	25	5
20	F	69	CAD	500 PO		25	10

Abbreviations CM= cardiomyopathy, CAD= coronary artery disease, HCTZ= hydrochlorothiazide, VD– valvular disease, PO= supplied orally, IV= supplied intravenously, TRIAM= triamterene, AMILO= amiloride, SPIRO= spironolactone

PATIENTS AND METHODS

After approval of the protocol by the local ethics committee, we selected 20 inpatients (six female, 14 male) with severe congestive heart failure (stage III (n=5) or IV (n=15) according to the New York Heart Association classification) who gave their informed consent for the study, which was performed between December 1989 and October 1994 All patients had an estimated oedematous mass of at least 5 kg and diuretic resistance Diuretic resistance was defined as a failure to lose weight and/or create a negative sodium balance despite bedrest, salt and fluid intake restricted, a diuretic regime of high dose furosemide (250 to 4000 mg daily dosage), administered orally or by continuous intravenous infusion, either or not in combination with potassium sparing diuretics (triamterene, amiloride and/or spironolactone) All studied patients had been using high dose furosemide for at least two weeks before the start of the study

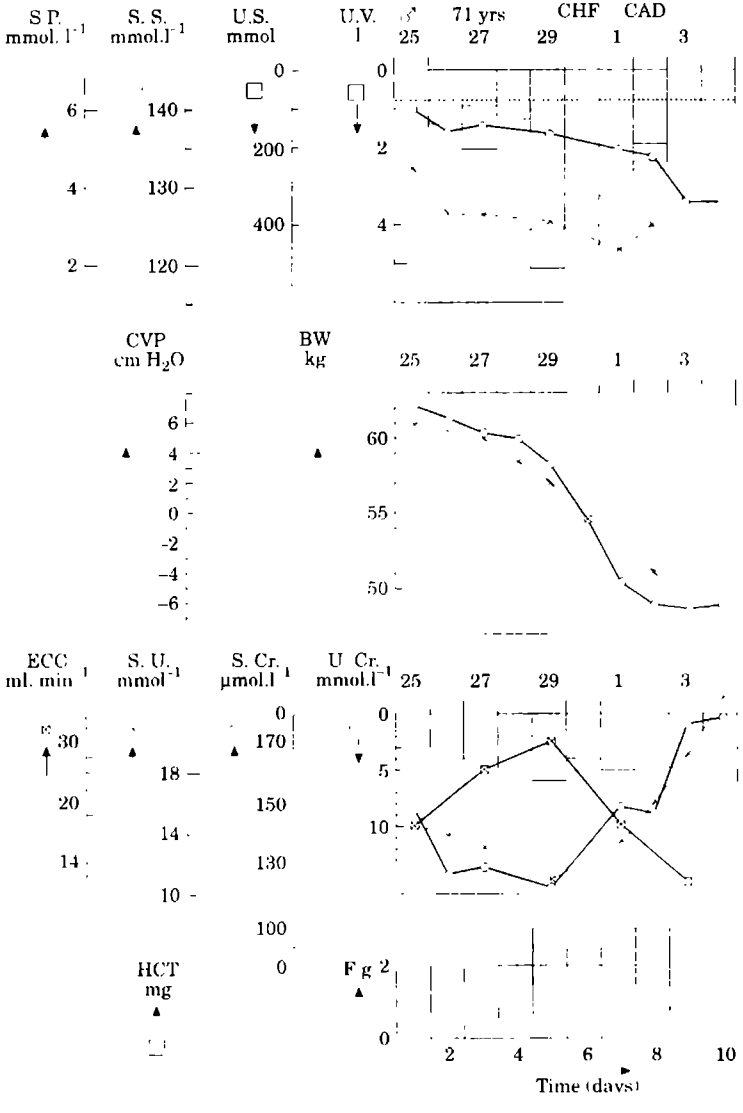
Differences in diuretic regimes between the patients occurred because they were referred for treatment by various departments During the study 12 patients used angiotensin converting enzyme inhibitors, in four patients enalapril was withdrawn soon after its introduction because of progressive renal impairment, while in two other patients enalapril caused symptomatic hypotension In two others we could retrospectively find no reason for withdrawal of angiotensin converting enzyme inhibition Ten patients used digoxin while none used dobutamin and/or low-dose dopamin
The relevant patient characteristics are presented in Table 1 Mean age was 70 8 years (range 30 to 86 years) and the mean body weight at the start of the study was 73 7 kg (55 2 to 96 8 kg) The underlying cause of heart failure was coronary artery disease (n=13), valvular disease (n=3), cardiomyopathy (n=3) and a combination of coronary artery disease and valvular disease (n=1) The left ventricle ejection fraction, estimated by cross sectional echocardiography, was less than 25% in all patients

During the entire study the daily dietary sodium intake was limited to 80 mmol and the fluid intake to 1500 ml Physical examination including measurement of body weight, supine and standing blood pressures, pulse rate, central venous pressure (determined by visual inspection of the neck veins [17]) and assessment of oedematous mass was performed daily Patients were daily interviewed for recognition of side effects The total daily output of urine was collected for creatinine, sodium, potassium chloride and protein measurements Daily blood samples were taken to determine serum sodium, potassium, chloride, bicarbonate albumin, uric acid, creatinine and urea
Monitoring was started at least 2 days days before administration and was continued until 2 days after withdrawal of hydrochlorothiazide Hydrochlorothiazide, either 50 or 100 mg (creatinine clearance >25 ml min^{-1} 1 73 m 100 mg hydrochlorothiazide, creatinine clearance <25 ml min^{-1} 1 73 m 50 mg hydrochlorothiazide), was added, leaving dosages of other medication (other diuretics included) unchanged Because three of the patients treated this way, showed signs of dehydration several days after withdrawal of hydrochlorothiazide, we decided to lower the starting dose to 25 mg hydrochlorothiazide in an attempt to avoid accumulation of hydrochlorothiazide In two patients the dosage of hydrochlorothiazide was increased during the study, because the at first chosen dose appeared to be ineffective Potassium supplements were given when serum potassium was lower than 3 5 mmol l^{-1}

Patients were treated with combination of high dose furosemide and hydrochlorothiazide during a period varying from 3 to 12 days When the hydration status of a patient was judged appropriate hydrochlorothiazide was stopped In two patients the hydrochlorothiazide medication was discontinued despite insufficient weight loss Because there was an important increase in natriuresis, we concluded that in these two patients weight loss was not achieved due to poor compliance with the dietary restrictions

Results are expressed as mean ±SD The Wilcoxon test was performed when the parameters before and after combined treatment with high dose furosemide and hydrochlorothiazide were compared

Figure 1. *Treatment results in a 71 year old man with chronic heart failure (CHF) caused by coronary artery disease (CAD, patient 2)*
The lowest panel shows the diuretic therapy: to 2 gram Furosemide (F) per day administered orally as the basic regimen, 100 mg hydrochlorothiazide (HCT) was added on 4 consecutive days. The fixed dose of spironolactone (50 mg) and amiloride (10 mg) is not shown.The upper panel shows the daily urine volume (UV), the natriuresis (US) and the course of the serum sodium (SS) and the serum potassium (SP), respectively. The dotted horizontal line represents the daily dietary sodium intake. Note that the lowest serum potassium value was 2.2 mmol. l^{-1} which increased after the potassium chloride intake was raised to 160 mmol per day, in addition to the potassium sparing diuretics. The upper middle panel shows the effects of the treatment on the bodyweight (BW) and the central venous pressure (CVP). The lower middle panel shows the daily creatinine excretion (UCr), the course of the serum creatinine (SCr) and urea (SU) levels, and endogenous creatinine clearance (ECC).



RESULTS

In the period preceding the combination therapy when only high dose furosemide was administered natriuresis was low in most patients indicating that sodium retaining mechanisms were activated However four patients showed a natriuresis of more than 125 mmol day without weight reduction (range 137 188 mmol 24 h) which can be explained by poor compliance with the dietary restriction The low natriuresis in the other patients (53 ±32 mmol 24 h' ranging from 7 to 100 mmol 24 h) confirms the diuretic resistance to high dose furosemide A typical example of the effect of the combination therapy is shown in Figure 1 The average weight reduction during the five days preceding the addition of hydrochlorothiazide was 0 6 ±1 2 kg (n=17) in three patients hydrochlorothiazide was added already 2 days after admission to the hospital because of the severity of the symptoms Patients were treated with combination of high dose furosemide and hydrochlorothiazide during a period varying from 3 to 12 days During this treatment period body weight reduction varied from 2 2 to 14 0 kg (6 7 ±3 3 kg) After withdrawal of hydrochlorothiazide the longest period of weight stabilization was in excess of 2 weeks in 16 patients During the use of combined diuretic therapy mean fractional sodium excretion increased from 3 5 ±3 2 % to 11 5 ±9 0 % ($p < 0.001$) (Table 2) After stopping the administration of hydrochlorothiazide fractional sodium excretion returned to the previous low level However in three patients using either 100 mg or 50 mg hydrochlorothiazide the increased natriuresis lingered on resulting in dehydration more than 2 days after stopping the combination therapy
All patients in this study had a reduced renal function Improvement of the hydration state of these patients induced a (not significant) reduction in endogenous creatinine clearance (32 7 ±22 5 ml min 1 73 m (range 4 4 to 110 7 ml min 1 73 m) prior to combination therapy vs 27 6 ±22 5 ml min 1 73 m (range 8 9 to 100 8 ml min 1 73 m after) In six patients correction of the hydration state resulted in an improvement of the endogenous creatinine clearance

Hypokalemia was an important side effect of the simultaneous administration of high dose furosemide and hydrochlorothiazide the elevated potassium excretion (65 ±33 mmol 24h' prior versus 115 ±55 during combined administration) resulted in hypokalemia in 15 patients (serum potassium lower than 3 5 mmol l) which could only be corrected by enlarging the potassium intake The lowest mean serum potassium measured during the combination therapy was 3 3 ±0 5 mmol l (ranging from 2 2 to 4 2 mmol l) It should be noted that before hydrochlorothiazide was added to the medication most of the patients already used potassium sparing diuretics (see Table 1) which failed to prevent the development of serious hypokalemia On average the patients were mildly hyponatremic (mean serum sodium 136 ±5 mmol l (reference value 138 to 144 mmol l') which (not significantly) aggravated during the combination therapy (134 ±8 mmol l')
Although serum uric acid concentration increased (not significantly) during the combined use of high dose furosemide and hydrochlorothiazide (0 67 ±0 26 mmol l' prior versus 0 79 ±0 27 mmol l' post $p < 0.01$) none of the patients developed attacks of gouty arthritis No side effects in particular hearing loss or tinnitus were recorded
No hypotensive episodes were observed during therapy

Eight patients were reallocated from NYHA class IV to III as a result of the treatment and one of five class III patients improved from class III to class II Fourteen patients were fit enough to be discharged from hospital Fifteen patients died with a mean survival of 122 ±129 days (ranging from 0 to 404 days) after termination of the high dose furosemide and hydrochlorothiazide treatment Five patients were still alive after a 1 year follow up period

Discussion

In the past 20 years the synergism between loop diuretics and thiazides has been described in several studies [4-13]. However, administration of loop diuretics in these studies were in relatively low doses (i.e. oral furosemide dosages lower than 500 mg. $24h^{-1}$) and to our knowledge this is the first study describing this synergism in patients with severe congestive heart failure and advanced renal failure showing diuretic resistance to high dose furosemide.

Table 2. *Effects of combined administration of high dose furosemide and hydrochlorothiazide*

	Before Treatment		During Treatment		After Treatment	
BW (kg)	73 7	± 13.9			67 0	± 13 3
BW reduction (kg day^{-1})	0 1	± 0 3**	1 3	± 0.8#		
UV (ml. $24\ h^{-1}$)	1899	± 958	3065	± 925#	2000	± 666
U_{sodium} (mmol. $24\ h^{-1}$)	85	± 58	206	± 84#	84	± 58
$U_{potassium}$ (mmol $24\ h^{-1}$)	65	± 33	115	± 55#	83	± 33*
$U_{chloride}$ (mmol $24\ h^{-1}$)	100	± 67	243	± 94#	116	± 65
FeNa (%)	3.5	± 3 2	11.5	± 9 0#	2.9	± 1 9
S_{sodium} (mmol l^{-1})	136	± 5			134	± 8
$S_{potassium}$ (mmol. l^{-1})	4.1	± 0.5	3.3	± 0 5#	4 2	± 0.7
$S_{chloride}$ (mmol l^{-1})	94	± 5			86	± 8#
$S_{bicarbonate}$ (mmol l^{-1})	28	± 2			33	± 4*
$S_{creatinine}$ (µmol. l^{-1})	148	± 69			177	± 78*
S_{urea} (mmol. l^{-1})	17	± 6			26	± 10#
ECC (ml min^{-1}. $1.73m^{-2}$)	32 7	± 22 5			27 6	± 22 5
$S_{albumin}$ (g l^{-1})	33.0	± 5 2			35.6	± 3.9*
$S_{uric\ acid}$ (mmol. l^{-1})	0 67	± 0 26			0.79	± 0.27†

Abbreviations: BW= body weight; UV= urine volume; U_{Sodium}, etc= urine electrolyte excretion; FeNa= fractional sodium excretion; ECC= endogenous creatinine clearance; S_{Sodium}, etc= serum concentrations

Results are mean ± standard deviation

** = $p < 0.05$, † = $p < 0.01$, # = $p < 0\ 001$, compared to before treatment with the Wilcoxon-test*

*** = n= 17*

The value of serum potassium during treatment represents the nadir of serum potassium during treatment. Administration of potassium supplements was started at a serum potassium value of 3 5 mmol l^{-1}

Under physiological conditions, approximately 25% of the filtered NaCl is reabsorbed in the loop of Henle, while 5% to 10% of the filtered NaCl load is reabsorbed in the distal tubule. However, the distal tubules have the ability to increase NaCl transport capacity when the delivered load of NaCl in this segment of the nephron increases [18-20]. Furosemide acts from the tubular lumen on the thick ascending limb of the loop of Henle and blocks the major part of the sodium reabsorbing capacity in this part of the nephron. As a result, more sodium is delivered to the distal parts of the nephron. In rats a chronic increment of the sodium delivery to the distal tubules appeared to induce hyperplasia of the cells and an increase of the sodium transport capacity in this segment [18,21,22]. It was shown that the sodium retaining capacity of the distal convoluted tubule was increased substantially after chronic use of loop diuretics and this seems to be an important cause of diuretic resistance [18,19,21,22].

Administration of high dose furosemide, preferably given as a continuous intravenous pump infusion, has been demonstrated to be a safe, efficient and controllable method of overcoming diuretic resistance to usually recommended doses (40 to 250 mg daily dosage) in chronic heart failure [2,3] The patients presented here all used high doses of furose mide (at least 250 mg daily), administered either orally or by continuous intravenous pump infusion, for at least 2 weeks, prior to combined use of high dose furosemide and hydrochlorothiazide During this phase, fractional sodium excretion was low in all patients, reflecting diuretic resistance It is also possible that diuretic resistance to high dose furosemide was the result of a decreased tubular excretion of furosemide, because we did not measure renal furosemide excretion In an animal experimental study it was shown that triamterene (and not amiloride or spironolactone) inhibits the tubular secretion of furosemide in a non-competetive manner [23] However, in the latter study, as well as in any of the studies on the coadministration of furosemide and triamterene in humans, this coadministration resulted in increased natriuresis [24,25] Therefore, it is unlikely that administration of triamterene together with high dose furosemide (n=7) will attribute to the diuretic resistance to high dose furosemide, as observed in the patients in this study Another possible cause for this diuretic resistance to high dose furosemide could be a reduced response in the loop of Henle However, the striking natriuretic response during combined use of high dosages of furosemide and hydrochlorothiazide in the patients presented here suggests that these furosemide doses are really able to reduce sodium reabsorption in the loop, even after prolonged use
In most of the studies describing the synergism between loop diuretics and thiazides, the former was combined with metolazone, a diuretic agent which is registered in only a few countries in Europe Metolazone is structurally related to the benzothiadiazines, with pharmacologic effects similar to hydrochlorothiazide [14,26] The major action of hydrochlorothiazide, like other thiazides, is from the luminar surface on the distal convoluted tubule Used as monotherapy, hydrochlorothiazide has no significant diuretic effect in patients with a considerably impaired renal function (endogenous creatinine clearance lower than 30 ml min 1 73m^{-2}) [15,26] One patient was subsequently treated with high dose furosemide alone, hydrochlorothiazide alone and a combination of high dose furosemide and hydrochlorothiazide (data not shown) Only the latter treatment resulted in an increased natriuresis

For these reasons, it seems unlikely that hydrochlorothiazide could by itself account for the natriuresis during the period of combined use of furosemide and hydrochlorothiazide in the patients presented Therefore, it is most probably the increased sodium reabsorbing capacity of the distal tubules and the collecting ducts in these patients that causes a diminished natriuretic response to high dose furosemide Evidence for the presence of this mechanism in humans was found in a previous study [27] Animal studies showed that even the increased sodium reabsorbing capacity of the distal tubule after chronic furosemide treatment could be almost completely blocked by thiazides [19,28]
Thus, the simultaneous administration of high dose furosemide and hydrochlorothiazide leads to a decreased sodium reabsorbtion in the loop of Henle and to a block of the increased sodium transport capacity in the distal tubule resulting in a significantly increase in fractional sodium excretion

The addition of hydrochlorothiazide in patients after chronic administration of loop diuretics (all patients in this study used high dose furosemide for at least 2 weeks) instead of simultaneous introduction of the two diuretic drugs might be even more powerful because of the increased sodium reabsorbing capacity of the distal tubule in these patients This increased reabsorbing capacity could also explain why hydrochlorothiazide is still effective in those patients with a reduction of the renal function below the level where thiazides as monotherapy are reported to become ineffective This observation is confirmed by the results of a recent study, showing that coadministration of thiazides increased efficacy of loop diuretics in patients with advanced renal failure [16]

In this study we did not analyze the effects of addition of a diuretic acting specifically on the proximal tubule to furosemide and hydrochlorothiazide on natriuresis In some of our patients we observed that the natriuretic effect of the combination of diuretics described persisted some days after administration of hydrochlorothiazide was stopped Three patients showed signs of dehydration some days after withdrawal of hydrochlorothiazide and required intravenous rehydration The reason for this prolonged effect might be the reduced renal clearance of hydrochlorothiazide in these patients (who all used 50 mg or 100 mg hydrochlorothiazide) with an impaired renal function resulting in a longer half life and accumulation of hydrochlorothiazide [26] A better cardiac output after amelioration of the hydration state or a stronger osmotic diuretic effect of the higher serum urea are other possible explanations for the improved natriuresis after the combined treatment

It should be emphasized that the combination of high dose furosemide and hydrochlorothiazide should only be used under carefully controlled circumstances Besides side-effects like hyponatremia alkalosis dehydration and loss of renal function hypokalemia shoud be avoided most of all Daily clinical and laboratory examination should be performed until a new equilibrium has been achieved The (not significant) reduction in renal function can be caused by slight dehydration or by a direct effect of hydrochlorothiazide [29]

Since the appearance of ototoxic side effects is positively related to the plasma furosemide concentration, patients treated with intravenously administered high dose furosemide and a reduced renal function (and thus a reduced renal clearance of furosemide are at risk for ototoxicity [30] On the other hand in an earlier study on the use of high dose furosemide in chronic hemodialysis patients there were no audiometric signs of ototoxicity [31] To avoid ototoxic plasma concentrations the patients in this study were mainly treated orally and in all of those receiving furosemide intravenously furosemide was administered as a continuous infusion None of the patients in this study complained of hearing loss or tinnitus However, this study did not comprise an audiometric evaluation

Left ventricle performance was significantly reduced in all patients studied They all had end stage congestive heart failure with a very short life expectancy Whether survival was prolonged by combined use of high dose furosemide and hydrochlorothiazide which is merely a symptomatic therapy could not be proven because of the absence of a matched control group The quality of life was definitely improved by reducing peripheral oedema and avoiding symptoms of lung oedema as demonstrated by the reduction in NYHA class On the other hand this therapy may worsen the prognosis Although chronic diuretic therapy may lead to a decrease in the hyperactivity of the sympathetic nervous system [32], diuretic treatment will cause further stimulation of the renin angiotensinogen system, causing negative hemodynamic effects [33 35] To reduce these effects angiotensin converting enzyme inhibitors and diuretics should be used simultaneously whenever possible Furthermore diuretic therapy can be associated with cardiac arrest [36]

A further benefit of this combination therapy is that an overhydrated state could be treated without the use of invasive techniques such as hemofiltration hemodialysis or continuous ambulatory peritoneal dialysis for example to bridge a period to a heart transplantation as in one of the patients included in this study

In conclusion, we observed that high dose furosemide (500 to 4000 mg daily dosage) and hydrochlorothiazide have a powerful synergistic diuretic effect in patients with severe congestive heart failure showing diuretic resistance to high dose furosemide despite a significantly reduced renal function (mean endogenous creatinine clearance 32.7 ±22.5 ml. min.$^{-1}$.1.73m^{-2}). Because of its side effects this combination therapy should only be used in a carefully controlled setting and should be reserved for a selected group of patients not responsive to other diuretic regimes.

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References

1 Guidelines for the evaluation and management of heart failure a report of the American Heart Association Task Force on Practice Guidelines Circulation 1995 92 2764-2784
2 Gerlag PG van Meijel JJ High dose furosemide in the treatment of refractory congestive heart failure Arch Intern Med 1988 148 286 291
3 Witerer G Donaldson M High-dose frusemide for cardiac failure Lancet 1995 346 254
4 Olesen KH Dupont B Hensted Jensen J The combined diuretic action of quinethazone and furosemide in congestive heart failure A permutation trial test Acta Med Scand 1970 187 33 40
5 Gunstone RI Wing AJ Shani HG Njemo D Sabuka EM Clinical experience with metolazone in fifty two African patients synergy with frusemide Postgrad Med J 1971 47 789 793
6 Sigurd B Olesen KH Wennevold A The supra additive natriuretic effect addition of bendroflumethiazide and bumetanide in congestive heart failure Permutation trial tests in patients in long term treatment with bumetanide Am Heart J 1975 89 163 170
7 Ghose RR,Gupta SK Synergistic action of metolazone with "loop" diuretics Br Med J Clin Res Ed 1981 282 1432 1433
8 Epstein MR Tepp BA Hoffman A Levinson R Potentiation of furosemide by metolazone in refractory edema Curr Ther Res 1977 21 656 667
9 Brater DC Pressley RH Anderson SA Mechanisms of the synergistic combination of metolazone and bumetanide J Pharmacol Exp Ther 1985 233 70 74
10 Wollam GL Tarazi RC Bravo EL Dustan HP Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia Am J Med 1982 72 929 938
11 Kivinge A Field MJ Pawsey CC Yiannikas J Lawrence JR Attel WJ Metolazone in treatment of severe refractory congestive cardiac failure Lancet 1990 335 29-31
12 Oster JR Epstein M Smoller S Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention Ann Intern Med 1983 99 405-406
13 Channer KS McLean KA Lawson Matthew P Richardson M Combination diuretic treatment in severe heart failure a randomised controlled trial Br Heart J 1994 71 146 150
14 Puschett JB Clinical pharmacologic implications in diuretic selection Am J Cardiol 1986 57 6A 13A
15 Cody RJ Kubo SH Pickworth KK Diuretic treatment for the sodium retention of congestive heart failure Arch Intern Med 1994 154 1905-1914
16 Hisel D Schroter M Neubeck M Ritz E Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure Kidney Int 1994,46 482 488
17 Borst JGG Molhuysen JA Exact determination of the central venous pressure by a simply clinical method Lancet 1952 2 304 306
18 Ellison DH Velazquez H Wright FS Adaptation of the distal convoluted tubule of the rat Structural and functional effects of dietary salt intake and chronic diuretic infusion J Clin Invest 1989 83 113 126
19 Ellison DH Diuretic drugs and the treatment of edema from clinic to bench and back again Am J Kidney Dis 1994 23 623 643
20 Ellison DH The physiologic basis of diuretic synergism its role in treating diuretic resistance Ann Intern Med 1991 114 886-894
21 Kaissling B Stanton BA Adaptation of distal tubule and collecting duct to increased sodium delivery I Ultrastructure Am J Physiol 1988 255 F1256 F1268
22 Stanton BA Kaissling B Adaptation of distal tubule and collecting duct to increased Na delivery II Na+ and K+ transport Am J Physiol 1988 255 F1269 F1275
23 Dropot M Sorgel F Mutschler E Pharmacodynamics and pharmacokinetics of furosemide combinations with potassium retaining and thiazide like diuretics clearance and micropuncture studies Naunyn Schmiedebergs Arch Pharmacol 1986 333 457 461
24 van Meyel JJ Tan Y Smits P Russel FG van Ginneken CA Gribnau FW Comparison of the diuretic effect and absorption of a single dose of furosemide and free and the fixed combinations of furosemide and triamterene in healthy male adults Eur J Clin Pharmacol 1990 39 595 597
25 Funke Kupper AJ Lintelman H Huige MC Koolen JJ Liem KL Lustermans FA Cross over comparison of the fixed combination of hydrochlorothiazide and triamterene and the free combination of furosemide and triamterene in the maintenance treatment of congestive heart failure Eur J Clin Pharmacol 1986 30 341 343
26 Niemeyer C Hasenfuss G Wais U Knauf H Schafer Korting M Mutschler E Pharmacokinetics of hydrochlorothiazide in relation to renal function Eur J Clin Pharmacol 1983 24 661-665
27 Loon NR Wilcox CS Unwin RJ Mechanism of impaired natriuretic response to furosemide during prolonged therapy Kidney Int 1989 36 682 689
28 Ellison DH Velazquez H Wright FS Thiazide sensitive sodium chloride cotransport in early distal tubule Am J Physiol 1987 253 F546 F554
29 Knauf H Mutschler E [Diuretic therapy in renal insufficiency] Dtsch Med Wochenschr 1987 112 1785 1789
30 Rybak LP Ototoxicity of loop diuretics Otolaryngol Clin North Am 1993 26 829-844

31 van Olden RW van Mevel JJ Gerlag PG Acute and long term effects of therapy with high dose furosemide in chronic hemodialysis patients Am J Nephrol 1992 12 351 356
32 Bayliss J Norell M Canepa Anson R Sutton G Poole Wilson P Untreated heart failure clinical and neuroendocrine effects of introducing diuretics Br Heart J 1987 57 17 22
33 Ikram H Chan W Espiner J A Nicholls MG Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure Clin Sci 1980 59 443 449
34 Packer M Treatment of chronic heart failure Lancet 1992 340 92 95
35 Taylor SH Refocus on diuretics in the treatment of heart failure Eur Heart J 1995 16 (Suppl I) 7 15
36 Siscovick DS Raghunathan TE Psaty BM et al Diuretic therapy for hypertension and the risk of primary cardiac arrest N Engl J Med 1994 330 1852 1857

THE NATRIURETIC EFFECT OF FUROSEMIDE IS NOT PRESERVED BY COADMINISTRATION OF HYDROCHLOROTHIAZIDE IN HEALTHY VOLUNTEERS

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ABSTRACT

Aims: The study was designed to evaluate whether the decline in natriuresis during chronic administration of furosemide, can be avoided by coadministration of a thiazide drug

Methods: Urinary sodium excretion (mean ±SD) during 5 h after an intravenous injection of furosemide 40 mg was measured on three separate occasions without pre-treatment, and, - in a double-blind randomized crossover fashion,- after a two-week pretreatment period with a combination of furosemide 20 mg b i d taken orally and a single daily oral dose of placebo, and after a two-week pretreatment period with furosemide 20 mg b i d taken orally in addition to a single daily oral dose of hydrochlorothiazide 25 mg

Results: Pretreatment with furosemide reduced the mean natriuretic response to this drug (267 mmol (95% CI 252-282 mmol) without pretreatment vs 218 mmol (95% CI 194-242 mmol) after pre-treatment with furosemide and placebo ($p<0,05$)
This reduction could not be prevented by coadministration of hydrochlorothiazide (233 mmol (95% CI 217-249 mmol), $p<0,05$)

Conclusion: Coadministration of hydrochlorothiazide does not preserve the natriuretic effect of furosemide in healthy male volunteers

Introduction

It is well established that after chronic administration of furosemide, the natriuretic response diminishes [1-3] This decrease is often referred to as braking phenomenon [4] Adaptations in both the proximal tubule and the distal convoluted tubule contribute to the decline in natriuretic effect of furosemide Both animal and human studies indicate that the sodium reabsorbing capacity of the distal convoluted tubules increases during chronic furosemide administration [5-7] This increased sodium absorption may completely offset the natriuretic effect of loop diuretics, causing diuretic resistance

In animal studies it was shown that thiazide diuretics can block sodium transport capacity of the distal convoluted tubules completely, even after chronic furosemide administration Moreover, use of thiazides may inhibit the increase in sodium reabsorbing capacity of the distal convoluted tubules during chronic furosemide administration [8] This means that the development of diuretic resistance to loop diuretics may be prevented or postponed by concomitant administration of a thiazide Whether thiazides can actually limit the increase in sodium reabsorbing capacity of the distal convoluted tubules during chronic treatment with furosemide in humans is still unclear

Therefore we hypothesized that, if adaptations in the distal convoluted tubules contribute importantly to the decline of natriuresis during chronic administration of furosemide, the natriuretic response can be preserved by coadministration of a thiazide drug

Methods

Subjects

Seven healthy male volunteers ranging in age from 22 to 40 years (mean 29) participated in the study after approval of the Ethics Committee of University Hospital Nijmegen A routine biochemical assessment (including serum minerals, BUN, creatinine and uric acid) was performed at the start of each of the three parts of the study Results were within normal limits in all participants and no significant differences were observed between the determinations on each of the three study days Weight and blood pressure, also determined on each of the three study days, did not change either

Table 1 *Body weight, serum electrolytes, serum uric acid, BUN, creatinine clearance, and cumulative urinary excretion of sodium and furosemide (F) in a 5 h and 24 h urine sample, following intravenous administration of 40 mg furosemide without pretreatment, after a 14 day oral pretreatment with furosemide (20 mg b i d) and placebo, and after a 14 day oral pretreatment with furosemide (20 mg b i d) and hydrochlorothiazide (25 mg) Values are presented as mean ±SD*

	no pretreatment		pretreatment F + P		pretreatment F + HCTZ	
Body weight (kg)	80	±10	79	±10	81	±10
Serum Sodium (mmol l^{-1})	141	±1	139	±2	140	±2
Serum Potassium (mmol l^{-1})	4 0	±0 2	4 0	±0 2	3 9	±0 2
Serum Chloride (mmol l^{-1})	105	±2	105	±3	107	±3
Serum Calcium (mmol l^{-1})	2 27	±0 07	2 27	±0 07	2 24	±0 06
Serum Magnesium (mmol l^{-1})	0 81	±0 05	0 80	±0 05	0 84	±0 03
Serum uric acid (mmol l^{-1})	0 34	±0 04	0 38	±0 07	0 40	±0 11
Serum phosphate (mmol l^{-1})	1 04	±0 09	1 01	±0 09	0 95	±0 18
Serum urea (mmol l^{-1})	5 9	±0 9	6 0	±1 2	6 8	±0 8
Creatinine clearance (ml min^{-1})	126	±18	124	±14	129	±20
U_{Na} 5 h (mmol)	267	±20	218	±33*	233	±22*
U_{Na} 24 h (mmol)	304	±44	301	±52	312	±33
$U_{Furosemide}$ 5 h (mg)	28 5	±1 5	28 6	±1 0	28 0	±0 4
$U_{Furosimide}$ 24 h (mg)	28 0	±2 0	30 1	±1 3	29 8	±0 7

**p<0 05 vs no pretreatment*

During the study volunteers were not placed on a standard diet Volunteers were not allowed to drink coffee, tea or alcohol throughout the study days

Study protocol

The study was performed in a double-blind randomized placebo-controlled crossover fashion The study consisted of two treatment periods Subjects were randomized to receive either two oral doses of 20 mg furosemide (8 a m and 5 p m) and one single oral dose of placebo (8 a m), or two oral doses of 20 mg furosemide (8 a m and 5 p m) and one single oral dose of hydrochlorothiazide (25 mg) (8 a m) Medication was used for 14 days in each of the two arms of the study On day 15 no medication was used On day 16 after an initial bladder voiding 40 mg furosemide was injected intravenously as a bolus Urine was sampled by asking volunteers to void at 30, 60, 90, 120, 180, 240 and 300 minutes after administration of furosemide Urine losses of each period were replaced volume for volume by a combination of intravenous saline solution and tap water during the subsequent period After 5 h the subjects went home and collected urine from 5 to 24 h Sodium and furosemide concentrations were determined in each of the urine samples To prevent photochemical degradation of furosemide, urine samples were protected against light After a washout period of at least two weeks the crossover mode of treatment was performed in an identical way Adherence to the described regimen was checked by collection of urine samples over 24 h on day 2 and day 14 for measurement of furosemide and hydrochlorothiazide Hydrochlorothiazide concentrations were also determined in the urine samples over 24 h on day 16

In order to visualize the decline in the natriuretic response to furosemide after chronic treatment with this drug, we also investigated the natriuretic response to furosemide without pretreatment To this end, the natriuretic response to a single intravenous injection of furosemide 40 mg was investigated This test was separated from the treatment periods by at least two weeks
Urine furosemide concentrations and urine hydrochlorothiazide concentrations were measured according to previously described methods [9,10]
For the statistical evaluation, Student's *t* tests for paired data were used at the 5% significance level

RESULTS

Body weight, serum electrolytes (sodium, potassium, magnesium, calcium, phosphate), serum uric acid, creatinine clearance and urine furosemide recovery (both 5 h and 24 h) after intravenous bolus injection of furosemide on day 16 of the two treatment periods did not differ significantly from the baseline measurements (see also Table 1) The recovery of furosemide and hydrochlorothiazide in the 24 h urinary output confirmed compliance with the medication intake No traces of hydrochlorothiazide were detected in the urinary output on two treatment days

Figure 1 *Mean (±SD) cumulative urinary sodium excretion after intravenous injection of 40 mg furosemide in seven healthy volunteers Cumulative sodium excretion was measured at three separate occasions without pretreatment (Control), after oral pre treatment during two weeks with furosemide 20 mg b i d and one single daily dose of placebo (Furosemide + Placebo), and after oral pretreatment during two weeks with furosemide 20 mg b i d and one single daily dose of hydrochlorothiazide 25 mg (Furosemide + HCTZ)*

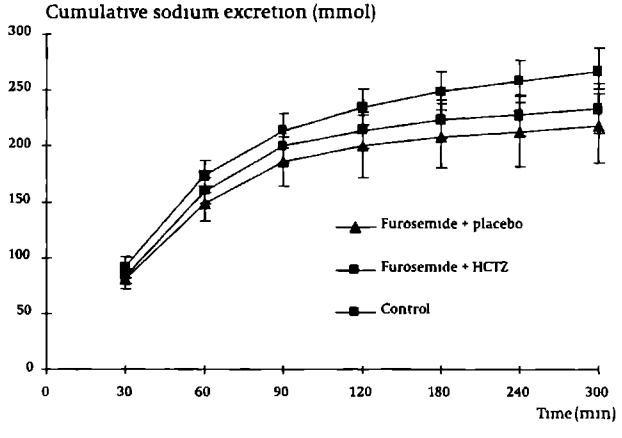

Figure 1 presents the cumulative natriuresis (mean +SD) during 5 h after intravenous administration of furosemide The mean urine sodium excretion decreased significantly after both treatment periods when compared with baseline measurements 267 mmol (95% CI 252-282 mmol) versus 218 mmol (95% CI 194-242 mmol, $p<0,05$) after pretreatment with furosemide and placebo and 233 mmol (95% CI 217-249 mmol, $p<0$ 05) after pretreatment with furosemide and hydrochlorothiazide Urine sodium excretion after intravenous bolus injection of furosemide did not differ significantly, when comparing the two pretreatment schedules

Discussion

This study convincingly shows that chronic treatment with furosemide reduces the natriuretic response to this drug. This reduction in natriuretic effect could not be prevented by cotreatment with a thiazide diuretic. There are a number of possible explanations why in our study hydrochlorothiazide exerted no preservative effect on the natriuretic effect of furosemide. Firstly, two weeks of furosemide administration may indeed induce adaptation of the distal convoluted tubules in healthy subjects, leading to a decreased natriuretic response to furosemide. However, 25 mg of hydrochlorothiazide dosed once daily may be insufficient to prevent adaptation of the distal convoluted tubular cells in healthy volunteers. In clinical studies with patients, suffering from heart failure and treated chronically with furosemide, addition of 25 mg of hydrochlorothiazide caused a dramatic increase in natriuresis, consistent with the ability of hydrochlorothiazide to block the sodium reabsorption in the hypertrophied distal convoluted tubules of these patients [11-14]. However, neither these studies, nor any other human study proves that addition of hydrochlorothiazide may prevent adaptation of the distal convoluted tubules. Moreover, the dose-response relationship remains unknown.

Secondly, in our subjects alterations in sodium reabsorbing capacity of the distal convoluted tubules may not have occurred and the differences in natriuretic effects between the baseline measurements and the measurements following chronic administration may have been caused by mechanisms that are not influenced by the addition of hydrochlorothiazide, e.g. adaptations in the proximal tubule or in the cortical collecting tubule.

In animal studies examining the adaptation of the distal convoluted tubules during continuous infusion of furosemide, dramatic hypertrophy of cells of the distal convoluted tubules and increased sodium reabsorbing capacity was observed after one week of furosemide infusion [5,6]. In humans it is unknown how long and at which dose furosemide should be administered before these structural and functional changes in the distal convoluted tubules are induced. In one human study indirect data indicated the presence of functional adaptation of the distal convoluted tubules after one month of furosemide administration [7]. So it is possible that two weeks of furosemide administration may be too short to induce functional adaptation of the distal convoluted tubules.

Another explanation could be that the chosen dose schedule of furosemide may be inadequate. In animal studies furosemide was administered as a continuous infusion [6]. By giving furosemide as two single oral dosages the drug-free interval may become too long to induce an adaptation of the distal convoluted tubules. However, in the human study by *Loon et al* furosemide, administered as two separate oral doses (40 mg b.i.d.) obviously resulted in an increase of sodium reabsorbtion at a thiazide sensitive segment of the nephron such as the distal convoluted tubules [7].

Finally, adaptation of the distal convoluted tubules may have been missed if the process of adaptation is rapidly reversible. Because of the elimination half life of hydrochlorothiazide, natriuretic effects of furosemide could only be analyzed approximately 40 hr after the last administration of hydrochlorothiazide.

We conclude that in healthy volunteers the natriuretic effect of furosemide decreases after chronic administration. However, in this study coadministration of hydrochlorothiazide with furosemide did not prevent the decrease in the natriuretic response to furosemide.

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References

1 Hammarlund M,Paalzow LK Acute tolerance development to the diuretic effect of furosemide in the rat Biopharm Drug Dispos 1985 6 9 21

2 Ellison DH The physiologic basis of diuretic synergism: its role in treating diuretic resistance Ann Intern Med 1991 114 886 894

3 Brater DC Resistance to loop diuretics: Why it happens and what to do about it Drugs 1985 30 427 443

4 Wilcox CS Mitch WE Kelly RA et al Response of the kidney to furosemide I Effects of salt intake and renal compensation J Lab Clin Med 1983 102 450 458

5 Stanton BA Kaissling B Adaptation of distal tubule and collecting duct to increased Na delivery II Na+ and K+ transport Am J Physiol 1988 255 F1269 F1275

6 Ellison DH Velazquez H Wright FS Adaptation of the distal convoluted tubule of the rat Structural and functional effects of dietary salt intake and chronic diuretic infusion J Clin Invest 1989 83 113 126

7 Loon NR Wilcox CS Unwin RJ Mechanism of impaired natriuretic response to furosemide during prolonged therapy Kidney Int 1989 36 682-689

8 Morsing P Velazquez H Wright FS Ellison DH Adaptation of distal convoluted tubule of rats II Effects of chronic thiazide infusion Am J Physiol 1991,261 F137 F143

9 Russel FGM Tan Y Mevel van JJM Grubnau EWJ Ginneken van CAM Solid phase extraction of furosemide from plasma and urine and subsequent analysis by high performance liquid chromatography J Chromat 1989 496 234 241

10 Koopmans PP Tan Y van Ginneken C AM Grubnau EWJ High performance liquid chromatographic determination of 12 hydrochlorothiazide in plasma and urine J Chromat 1984 307 445 450

11 Dormans TPJ Gerlag PGG Combination of high dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure Eur Heart J 1996 17 1867 1874

12 Gunstone RF Wing AJ Shani HG, Njemo D Sabuka LM Clinical experience with metolazone in fifty two African patients synergy with frusemide Postgrad Med J 1971 47 789 793

13 Epstein MR Tepp BA Hollman A,Levinson R Potentiation of furosemide by metolazone in refractory edema Curr Ther Res 1977 21 656-667

14 Channer KS Richardson M Crook R Jones JV Thiazides with loop diuretics for severe congestive heart failure Lancet 1990 335 922 923

COMBINATION DIURETIC THERAPY IN SEVERE CONGESTIVE HEART FAILURE

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SUMMARY

Severe congestive heart failure is often characterized by fluid retention. A (chronic) state of overhydration influences has a negative influence on both the quality of life and the prognosis of these patients. Therefore, the use of diuretics remains a cornerstone in the treatment of heart failure. However, diuretic resistance, a failure to correct the hydration state adequately with the use of conventional dosages of loop diuretics, is a frequently occurring complication in the treatment of advanced stages of congestive heart failure.

Several intra- and extrarenal mechanisms may be involved in the development of diuretic resistance. An important pathophysiological mechanism leading to diuretic resistance seen after chronic use of loop diuretics is the functional adaptation of the distal tubule. Studies in animals demonstrate that the sodium reabsorption capacity of this nephron segment increases significantly when the sodium delivery to this segment is augmented, as is the case during administration of loop diuretics.

The use of combinations of diuretics acting on different segments of the nephron appears to be an effective option in the treatment of diuretic resistance. Several combinations have been used, however, the combination of a loop diuretic and a thiazide drug acting on the distal tubule appears to be the most effective. However, since the use of this combination may lead to serious adverse effects such as hypokalemia, metabolic alkalosis and dehydration, careful monitoring of the patient on combination diuretic therapy is necessary.

INTRODUCTION

Heart failure is a major health problem [1,2], and its incidence is expected to further increase in the next decade [3] Since no curative therapy is currently available for the majority of patients, the goals of treatment are to improve quality of life and to postpone progression of the disease [4] Although important advances in the pharmacological treatment of heart failure have recently been achieved, it is still inevitable that a considerable number of patients will progress to the advanced stages of this disease

The clinical picture of advanced stages of heart failure is often dominated by the presence of oedema and congestion, causing symptoms of dyspnoea, fatigue, nausea and discomfort Moreover, chronic congestion contributes to further progression of the disease [5,6] For these 2 reasons, maintenance of an adequate state of hydration is very important This is usually achieved by use of loop diuretics in combination with a salt restriction and a limitation of physical activity However, as the disease progresses, oedema may reoccur despite these measures In some of these cases, the decrease in efficacy of diuretic therapy appears to be caused by diuretic resistance, a phenomenon that can be defined as the failure to create a negative sodium balance despite the use of conventional dosages of furosemide (frusemide) (250 mg per day or an equivalent amount of another loop diuretic), a sodium restricted diet (60 to 80 mmol sodium per day) and restriction of physical activity The mechanisms responsible for diuretic resistance are very diverse (Table 1) In decompensated heart failure, intestinal absorption of orally administered furosemide may be altered, causing inadequate concentrations of loop diuretic on the site of action [7] Decrease of renal perfusion due to various causes results in a decrease of the capacity of the proximal tubule to secrete furosemide and/or bumetanide into the urine [8] Endogenous acids and non-steroidal anti-inflammatory drugs compete with loop diuretics for secretion into the tubule by the organic acid pump in the proximal tubule [9]

In clinical practise the use of combinations of diuretics acting on different segments of the nephron, often referred to as sequential nephron blockade, has shown to be highly effective in the treatment of diuretic resistance in congestive heart failure [10] Recent studies give insight in to some of the pathophysiological mechanisms involved in diuretic resistance In this article, we focus on the mechanisms that explain the synergism of combinations of diuretic drugs in severe heart failure, indications for their use and adverse effects

MECHANISMS OF DIURETIC RESISTANCE

Under physiological conditions sodium reabsorption takes place in all segments of the nephron In the proximal tubule, 60 to 70% of the filtered sodium is reabsorbed, in the loop of Henle, the distal tubule and in collecting tubule 20 to 25%, 5 to 10% and only 3% of the filtered sodium, respectively, This means that more than 99% of the filtered sodium is usually reabsorbed in the tubular system [11] However, in heart failure, with or without diuretic therapy, these numbers are different Several mechanisms account for the varying contributions of the nephron segments to the sodium reabsorption

Sodium reabsorption in heart failure

In heart failure, the absolute amount of sodium that is filtered may be decreased due to reduced renal perfusion in a state of low cardiac output Secondly, heart failure is characterized by activation of both the renin-angiotensin system and the sympathetic stimulation In heart failure the filtration fraction is increased, which is mediated by vasoconstriction of the efferent arteriole

This vasoconstriction is mainly induced by an increased intrarenal production of angiotensin II [12] As a result, transcapillary hydrostatic pressure and oncotic pressure is decreased, causing increased sodium and water reabsorption in the proximal tubule Moreover, Angiotensin II may exert a direct sodium-retaining effect on the proximal renal tubule [13,14], and it increases sodium reabsorption indirectly in the collecting ducts by an upregulation of aldosterone secretion Although the use of angiotensin-converting enzyme (ACE) inhibitors in heart failure is advocated angiotensin II levels are often insufficiently decreased in patients with severe heart failure due to intolerance of adequate dosages of ACE-inhibitors

Catecholamines directly induce an increase of sodium reabsorption by several mechanisms they stimulate sodium reabsorption in the proximal tubules, indirectly stimulate this reabsorption by stimulation of renin release, and reduce renal perfusion as a result of their vasoconstrictive effects on the afferent arterial system [15-17] Other mechanisms that play a role in the development of volume overload are the stimulation of the cerebral thirst centre by angiotensin and the enhanced release of antidiuretic hormone in end stage heart failure [5]

Table 1 *Causes of treatment failures with conventional dosages of loop diuretics in patients with decompensated heart failure*

I noncompliance with medical regimen:

Nonadherence to sodium restriction
Nonadherence to drug regimen

II True diuretic resistance

II A Pharmacokinetic causes

Altered intestinal absorption of the loop diuretic
Decreased renal perfusion due to
- low cardiac output
- atherosclerosis, renal artery stenosis, cholesterol emboli
- hypovolemia
- decreased filtration fraction (e g due to use of ACE inhibitors or NSAIDs)

Reduced tubular secretion
- nefrologic pathology
- hypovolemia
- competitive inhibition by NSAIDs, probenecid, endogeneous acids (renal insufficiency, gout)

II B Pharmacodynamic causes

Adaptation of distal convoluted tubule to chronic use of loop diuretics

Abbreviations ACE=angiotensin-converting enzyme, NSAID=non-steroidal anti inflammatory drug

In addition to activation of sodium retaining mechanisms, the natriuretic effects of atrial natriuretic peptide are attenuated in heart failure [5]

These mechanisms may all contribute to the sodium retaining state (and thus the development of oedema) that characterizes the advanced stages of congestive heart failure Due to activation of the sodium retaining mechanisms in severe heart failure, loop diuretics are less effective, and so dose-response curves of loop diuretics are shifted downward and to the right in patients with congestive heart failure [18] In a number of these patients, an extreme activation of the described sodium retaining mechanisms may thus cause diuretic resistance

Pharmacodynamic effects of diuretics

The administration of loop diuretics has a number of effects

- Loop diuretics inhibit the Na K-2Cl cotransporter from the luminal site of the thick ascending limb of the loop of Henle, thereby blocking the sodium reabsorption in this segment of the nephron almost completely Usually an increased urinary sodium excretion will follow

- When the commonly used intermittent dosing schedules of loop diuretics are used, no diuretic drug is available at the site of action during a considerable part of the dosing interval In this so called 'post-diuretic phase' sodium is avidly reabsorbed, resulting in a rebound sodium retention in the nephron Moreover, the natriuretic effect of loop diuretic is attenuated after repeated dosages while the patient is on a salt restricted diet [19] Both these observations can not completely be explained by enhancement of sympathetic stimulation and further increase of the activity of the renin-angiotensin-aldosterone axis [20] However to prevent activation of the latter in heart failure, diuretics are combined with ACE-inhibitors, whenever possible

- By blocking the sodium reabsorption in the loop segment, loop diuretics cause an increase in tubular sodium concentration at the level of the distal convoluted tubule [11] In studies in rats, it was shown that high rates of sodium delivery to the distal convoluted tubule, induced by chronic furosemide infusion caused a hypertrophy of this segment of the nephron that was associated with an increased capacity to reabsorb sodium [18-20] These morphological and functional changes were observed after one week of furosemide infusion Although the exact mechanisms involved in these structural and functional adaptations are unknown, it was hypothesised that cellular sodium concentrations regulate tubular cell growth directly [24] Data obtained from a human study indicate that these adaptations to chronic furosemide administration also occur in humans [25] This mechanism may explain why the diuretic efficacy of loop diuretics after chronic administration attenuates in heart failure

Thiazides are able to block essentially all sodium reabsorbtion in the distal convoluted tubule, even after hypertrophy has occurred [26] This means that thiazides are highly effective when both the sodium reabsorbing capacity of the distal tubule and the sodium delivery to the distal tubule are increased as is the case after chronic administration of a loop diuretic It explains the synergistic natriuretic effect of loop diuretics and thiazides On the other hand, chronic administration of thiazides induces a reduction of the sodium reabsorption capacity in this part of the nephron [23] This observation indicates that functional adaptations due to increased sodium delivery in the distal tubule may be avoided or corrected by administration of thiazides

What diuretic combinations are useful?

Many different combinations of diuretic drugs have been described in the past three decades In nearly all of the described combinations loop diuretics form the basis of combination therapy Although the two most widely used loop diuretics, furosemide and bumetanide, differ with respect to pharmacokinetic properties, the difference in overall response to equipotent amounts of these drugs is subtle and probably of no clinical relevance in patients with congestive heart failure[27] In the following we discuss most of the possible combinations of drugs Diuretic drugs currently available and their site of action in the nephron include

- acetazolamide, theophylline and mannitol (proximal tubule),
- ethacrynic acid, furosemide, bumetanide, torasemide and piretanide (loop of Henle),
- hydrochlorothiazide, chlorothiazide, bendroflumethiazide, chlorthalidone and metolazone (distal convoluted tubule),
- amiloride, triamterene and spironolactone (collecting duct)

As a general rule, combinations of two diuretic drugs acting on the same segment of the nephron will not result in a synergistic effect and therefore should not be combined

Loop and proximal diuretics

Few studies have been done examining the combination of a loop diuretic with a drug acting on the proximal tubule *Sigurd and Oleson* established that the proximally acting phosphodiesterase inhibitor aminophylline (theophylline ethylenediamine) in combination with long term treatment with bumetanide 2mg 3times daily in patients with congestive heart failure, produced a synergistic effect Addition of the proximally acting diuretic drug appeared to be superior to monotherapy with bumetanide given in a daily dosage of up to 6 mg [28] It should be noted that theophylline has not only diuretic properties, but also inotropic and chronotropic effects, which may contribute to the improvement of natriuresis in congestive heart failure However, the use of theophylline as a diuretic drug in heart failure may be limited by its chronotropic effects
In a recent study, it was established that coadministration of the carbonic anhydrase inhibitor acetazolamide, to heart failure patients with an inadequate natriuretic response to furosemide, was very effective [29]
These studies clearly show that the combination of a loop diuretic and a diuretic acting on the proximal tubule has synergistic diuretic effects in the acute phase However, no information is currently available on the efficacy of this combination when applied on a long term basis Moreover, It has not been established whether treatment with diuretics acting on the proximal tubule induces structural and functional changes in the down stream segments of the nephron

Loop diuretic and diuretic acting on the distal convoluted tubule

Many clinical studies report the synergistic effect of loop diuretics and thiazides or thiazide-like drugs in congestive heart failure [30-42] The guidelines of the American College of Cardiology /American Heart Association and the European Society of Cardiology on the treatment of heart failure recommend the use of this combination in case of diuretic resistance to a loop diuretic [1,43] As described above, the mechanism behind this synergism consists of the functional adaptations in the distal tubule following chronic administration of a loop diuretic [21,23,44] Many different thiazide and thiazide-like drugs have been used in combination with a loop diuretic Most of the published data relates to metolazone However, comparisons of thiazides with respect to their efficacy when used in combination therapy are sparse [45] On the basis of the available literature, thiazide drugs are equally effective

Used as monotherapy, thiazides are ineffective at glomerular filtration rates <30 ml min^{-1} However, coadministration of thiazides increases the efficacy of a loop diuretic in patients both with and without renal failure [35,41,42]

Loop diuretic and collecting duct tubule

Addition of triamterene or amiloride to a loop diuretic appears to have a limited effect on natriuiesis, probably because the sodium reabsorbing capacity of the collecting duct tubule of the nephron is small [11] On the other hand, coadministration of spironolactone (100 mg once a day) in congestive heart failure refractory to high dose bumetanide (10 mg per day), improved natriuresis significantly [46]

INDICATIONS FOR COMBINATIONS OF DIURETICS IN HEART FAILURE

In case of an inadequate response to diuretics in a patient suffering from heart failure a stepwise evaluation may help to find the cause of it

- Is the patient really overhydrated? A careful physical examination usually will answer this question During long term follow-up of a patient body weight is a very important parameter

- Ensure that there are no causes for oedema other than heart failure Hypoalbuminemia and other causes of heart failure, that need to be treated by other means (e g valvular disease or (constrictive) pericarditis) need to be excluded

- How is patient compliance to the medical regimen? It should be emphasized that adherence to a sodium-restricted diet is essential for the success of diuretic treatment This can be evaluated by determination of urinary sodium excretion If the urinary sodium excretion exceeds 100 mmol per day, without any concurrent body weight change, poor compliance with dietary therapy (and not diuretic resistance) is the cause of persistent oedema When poor compliance with drug intake is suspected,urinary drug excretion may be evaluated

- When noncompliance with the medical regimen is excluded, diuretic resistance is identified as the cause of therapy-resistant oedema

When diuretic resistance is present, improvement of the efficacy of the loop diuretic prescribed could be the next step

- Increase the dosage of the loop diuretic Large doses of loop diuretics (daily oral dosage up to 2000 mg) have shown to overcome diuretic resistance [47] Many clinicians feel reluctant to use such high dosages of diuretics, because of the potential for ototoxicity [48] In our experience, however, irreversible ototoxic side effects only occurred after coadministration of aminoglycosides In addition, audiometric evaluations have revealed that short term completely reversible ototoxic side effects occurred significantly more frequent after administration of intravenous bolus injections of furosemide than after administration of an equal dosage as a continuos intravenous infusion (*Dormans et al*, unpublished data)

- Administer the loop diuretic two or three times a day This strategy reduces the drug-free intervals, and thus the post-diuretic sodium retention [49,50] However, inconvenience due to frequent nocturnal voiding should be avoided

When the effect of these steps is insufficient several therapeutic strategies are to be considered

- Intravenous administration of a loop diuretic increases its bioavailability The amount of drug delivered to the site of action will be increased Because the time course of delivery is an important determinant of the efficacy, a continuous intravenous infusion is more efficacious than intravenous bolus injections [51 53] In a recent study it was reported that administration of bumetanide as a continuos infusion triggered less braking than an equal dosage administered as a seperate intravenous bolus injection [54] In other words, the diuretic efficacy is better preserved when using a continuous intravenous infusion However, intravenous administration usually makes admission to a hospital necessary

- Combinations of diuretics are highly effective, but may cause severe metabolic disturbances Hypokalemia must be avoided Other important adverse drug effects are hyponatremia, dehydration and metabolic alkalosis This makes frequent control and monitoring of serum electrolytes necessary, especially in the first weeks after addition of the thiazide to the loop diuretic In addition, it should be remembered that use of combination diuretic therapy may cause too rapid a loss of fluid resulting in hypotension and dehydration A too vigorous dehydration may result in a temporary decrease of the effective circulatory volume This may cause hypotension and deterioration of renal function Therefore, in addition to serum electrolytes and body weight, renal function and blood pressure also should be monitored Finally, noninvasive assessment of the central venous pressure is of value as a valid indicator of the state of hydration

- It is necessary to tailor the treatment to each individual patient to achieve a gradual reduction of oedema For these reasons, hospital admission of the patient is pre ferred when adding a thiazide drug to a loop diuretic

Although it is generally advocated to increase the dosage of the loop diuretic to the max imum recommended dosage (240 mg furosemide per day or an equivalent dosage of another loop diuretic), other strategies have been proven to be succesful, firstly, the addition of a thiazide to a low dosage of a loop diuretic in case of an inadequate response to the latter [55] The theoretical advantage of early introduction of a thiazide in the course of development of diuretic resistance is that the thiazide may avoid functional and structural adaptations in the distal convoluted tubule or reverse them at an early stage [23] A variation on this treatment schedule is the intermittent addition of thiazides, e g twice a week Titration can be achieved using body weight changes as the most important parameter [10] Secondly, monotherapy with high dose furosemide (daily dosages varying from 250-4000 mg) has been shown to be safe and effective [47,56] Addition of a thiazide to these high dosages furosemide has been shown to be a powerful diuretic tool in patients with severe congestive heart failure [42]

In cases where even the combined use of a loop diuretic and a thiazide fails to reduce the extracellular volume to the desired level, there are still some alternatives By addition of a inotropic drug, e g dobutamine or milrinone, improvement of cardiac output can be achieved This may lead to an increase of the amount of filtered sodium Secondly, extracorporal techniques (hemofiltration, hemodialysis, peritoneal dialysis) may lead to short term improvement and restoration of diuretic responsiveness [57-59] However, in our opinion the results of the chronic intermittent use of hemofiltration and hemodialysis were disappointing, and therefore should be reserved for remediable cases of heart failure or as a bridge to heart transplantation [60]

Conclusions

The combined use of a loop diuretic and a diuretic acting on the distal convoluted tubule has been shown to be a very powerful tool in the treatment of diuretic resistance to conventional therapy in congestive heart failure. However, adverse effects, especially hypokalemia, necessitate frequent control and monitoring of serum electrolytes and the clinical condition of the patient after initiation of this therapy. An important mechanism behind this diuretic synergism is the functional adaptation of the distal convoluted tubule after chronic administration of loop diuretics.

References

1 Guidelines for the evaluation and management of heart failure: a report of the American Heart Association Task Force on Practice Guidelines. Circulation 1995; 92: 2764-2784
2 Reitsma JB, Mosterd A, Craen de AJM, et al. Increase in hospital admission rates for heart failure in the Netherlands: 1980-1993. Heart 1996; 76: 388-392
3 Rodeheffer RJ, Jacobsen SJ, Gersh BJ, et al. The incidence and prevalence of congestive heart failure in Rochester, Minnesota. Mayo Clin Proc 1993; 68: 1143-1150
4 Packer M. Treatment of chronic heart failure. Lancet 1992; 340: 92-95
5 Packer M. Pathophysiology of chronic heart failure. Lancet 1992; 340: 88-92
6 Stevenson LW, Dracup KA, and Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. Am J Cardiol 1989; 63: 461-464
7 Vasko MR, Cartwright DB, Knochel JP, et al. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985; 102: 314-8
8 Brater DC, Seiwell R, Anderson S, et al. Absorption and disposition of furosemide in congestive heart failure. Kidney Int 1982; 22: 171-6
9 Chennavasin P, Seiwell R, Brater DC. Pharmacokinetic-pharmacodynamic analysis of the indomethacin-furosemide interaction in man. J Pharmacol Exp Ther 1980; 215: 77-81
10 Cody RJ, Kubo SH, and Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. Arch Intern Med 1994; 154: 1905-1914
11 Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 1991; 114: 886-894
12 Kelly RA, and Smith TW. Drugs used in the treatment of heart failure. In: Heart Disease: a textbook of cardiovascular medicine, edited by Braunwald E. Philadelphia: WB Saunders Co; 1997: 471-491
13 Hall JE. Control of glomerular filtration rate and sodium excretion by angiotensin II. Fed Proc 1986; 45: 1431-1436
14 Blantz RC. The glomerular and tubular actions of angiotensin II. Am J Kidney Dis 1987; 10 (suppl I): 2-10
15 Mancia G. Neurohumoral activation in congestive heart failure. Am Heart J 1990; 120: 1532-1537, 1990
16 Mancia G. Sympathetic activation in congestive heart failure. Eur Heart J 1990; 11 Suppl A: 3-11
17 Kon V, Yared A, and Ichikawa I. Role of sympathetic nerves in mediating hypoperfusion of renal cortical microcirculation in experimental congestive heart failure and acute extracellular volume depletion. J Clin Invest 1985; 76: 1913-1920
18 Brater DC, Chennavasin P, Seiwell R. Furosemide in patients with heart failure: shift in dose-response curves. Clin Pharmacol Ther 1980; 28: 182-186
19 Wakelkamp M, Alvan G, Gabrielsson J, et al. Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration. Clin Pharmacol Ther 1996; 60: 75-88
20 Wilcox CS, Guzman NJ, Mitch WI, et al. Na+, K+, and BP homeostasis in man during furosemide: effects of prazosin and captopril. Kidney Int 1987; 31: 135-141
21 Kaissling B, and Stanton BA. Adaptation of distal tubule and collecting duct to increased sodium delivery. I. Ultrastructure. Am J Physiol 1988; 255: F1256-F1268
22 Stanton BA, and Kaissling B. Adaptation of distal tubule and collecting duct to increased Na delivery. II. Na+ and K+ transport. Am J Physiol 1988; 255: F1269-F1275
23 Morsing P, Velazquez H, Wright FS, and Ellison DH. Adaptation of distal convoluted tubule of rats. II. Effects of chronic thiazide infusion. Am J Physiol 1991; 261: F137-F143
24 Stanton BA, and Kaissling B. Regulation of renal ion transport and cell growth by sodium. Am J Physiol 1989; 257: F1-10
25 Loon NR, Wilcox CS, and Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int 1989; 36: 682-689
26 Ellison DH, Velazquez H, and Wright FS. Thiazide-sensitive sodium-chloride cotransport in early distal tubule. Am J Physiol 1987; 253: F546-F554
27 Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney Int 1984; 26: 183-189
28 Sigurd B, and Olesen KH. The supra-additive natriuretic effect: addition of theophylline-ethylenediamine and bumetanide in congestive heart failure. Permutation trial tests in patients in long-term treatment with bumetanide. Am Heart J 1977; 94: 168-174
29 Knauf H, and Mutschler E. Sequential nephron blockade breaks resistance to diuretics in edematous states. J Cardiovasc Pharmacol 1997; 29: 367-372
30 Olesen KH, Dupont B, and Hemsted-Jensen F. The combined diuretic action of quinethazone and furosemide in congestive heart failure. A permutation trial test. Acta Med Scand 1970; 187: 33-40
31 Gunstone RT, Wing AJ, Shani HG, Njemo D, and Sabuka EM. Clinical experience with metolazone in fifty-two African patients: synergy with frusemide. PostgradMed J 1971; 47: 789-793
32 Sigurd B, Olesen KH, and Wennevold A. The supra-additive natriuretic effect: addition of bendroflumethiazide and bumetanide in congestive heart failure. Permutation trial tests in patients in long-term treatment with bumetanide. Am Heart J 1975; 89: 163-170
33 Ghose RR, and Gupta SK. Synergistic action of metolazone with loop diuretics. Br Med J Clin Res Ed 1981; 282: 1432-1433
34 Epstein M, Lepp BA, Hoffman A, and Levinson R. Potentiation of furosemide by metolazone in refractory edema. Curr Ther Res 1977; 21: 656-667
35 Wollam GL, Tarazi RC, Bravo EL, and Dustan HP. Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. Am J Med 1982; 72: 929-938

36 Brater DC Pressley RH and Anderson SA Mechanisms of the synergistic combination of metolazone and bumetanide J Pharmacol Exp Ther 1985 233 70-74
37 Reubi FC Combination diuretic drug therapy Cardiovasc Clin 1971 2 197 210
38 Oster JR Epstein M and Smoller S Combined therapy with thiazide type and loop diuretic agents for resistant sodium retention Ann Intern Med 1983 99 405 406
39 Kivinge A Field MJ Pawsey CC Yiannikas J Lawrence JR and Arter WJ Metolazone in treatment of severe refractory congestive cardiac failure Lancet 1980 335 29 31
40 Channer KS Richardson M Crook R and Jones JV Thiazides with loop diuretics for severe congestive heart failure Lancet 1990 335 922 923
41 Hisel D Schroter M Neubeck M and Ritz E Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure Kidney Int 1994 46 482-488
42 Dormans TPJ and Gerlag PGG Combination of high dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure Eur Heart J 1996 17 1867 1874
43 The Task Force of the Working Group on Heart Failure of the European Society of Cardiology The treatment of heart failure Eur Heart J 1997 18 736 753
44 Ellison DH Velazquez H and Wright FS Adaptation of the distal convoluted tubule of the rat Structural and functional effects of dietary salt intake and chronic diuretic infusion J Clin Invest 1989 83 113 126
45 Channer KS McLean KA Lawson Matthew P and Richardson M Combination diuretic treatment in severe heart failure Lancet randomised controlled trial Br Heart J 1994 71 146 150
46 van Vliet AA Donker AJ Nauta JJ and Verheugt FW Spironolactone in congestive heart failure refractory to high dose loop diuretic and low dose angiotensin converting enzyme inhibitor Am J Cardiol 1993 71 21A 28A
47 Gerlag PG van Meyel JJ high dose furosemide in the treatment of refractory congestive heart failure Arch Intern Med 1988 148 286 91
48 Rybak LP Furosemide ototoxicity clinical and experimental aspects Laryngoscope 1985 95 1 14
49 Brater DC Resistance to loop diuretics Why it happens and what to do about it Drugs 1985 30 427 443
50 Hammarlund Udenaes M and Benet LZ Furosemide pharmacokinetics and pharmacodynamics in health and disease an update J Pharmacokinet Biopharm 1989 17 1 46
51 Kaojarern S Day B and Brater DC The time course of delivery of furosemide into urine an independent determinant of overall response Kidney Int 1982 22 69 74
52 Rudy DW Voelker JR Greene PK Espatza LA and Brater DC Loop diuretics for chronic renal insufficiency a continuous infusion is more efficacious than bolus therapy Ann Intern Med 1991 115 360-366
53 Dormans TPJ van Meyel JJM Gerlag PGG Tan Y Russel FGM and Smits P Diuretic efficacy of high dose furosemide in severe heart failure bolus injection versus continuous infusion J Am Coll Cardiol 1996 28 376 382
54 Ferguson JA Sundblad KJ Becker PK et al Role of duration of diuretic effect in preventing sodium retention Clin Pharmacol Ther 1997 62 203-8
55 Knauf H and Mutschler L Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure J Cardiovasc Pharmacol 1995 26 394-400
56 van Meyel JJ Smits P Dormans T Gerlag PG Russel FG and Grobnan FW Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance J Intern Med 1994 235 329 334
57 Simpson IA Rae AP Simpson K et al Ultrafiltration in the management of refractory congestive heart failure Br Heart J 1986 55 344-347
58 Rimondini A Cipolla CM Della Bella P et al Hemofiltration as short term treatment for refractory congestive heart failure Am J Med 1987 83 43 48
59 Rubin J and Ball R Continuous ambulatory peritoneal dialysis as treatment of severe congestive heart failure in the face of chronic renal failure Report of eight cases Arch Intern Med 1986 146 1533 1535
60 Dormans TPJ Huige RMC and Gerlag PGG Chronic intermittent haemofiltration and haemodialysis in end stage chronic heart failure with oedema refractory to high dose frusemide Heart 1996 75 349 351

CHAPTER EIGHT

VASCULAR EFFECTS OF LOOP DIURETICS

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Abstract

Although it is generally believed that the beneficial effect of loop diuretics is the result of a rapid increase in diuresis, substantial evidence, from a large number of in vitro and in vivo experiments, has accumulated, showing that administration of furosemide causes direct vascular effects, which probably contribute to its acute clinical effects

Several mechanisms are involved in the vascular response to loop diuretics The role of the renin-angiotensin-aldosterone axis, prostaglandins and the direct vascular effects of loop diuretics on both the arterial and venous parts of the vasculature are discussed

IINTRODUCTION

Diuretic therapy has proved to be effective in the treatment of acute and chronic heart failure The potent loop diuretics furosemide and bumetanide are frequently used in the treatment of disease states characterized by fluid and sodium retention After intravenous administration of furosemide, clinical relief of symptoms often precedes the increase in diuresis in patients with acute heart failure suggesting the presence of an extrarenal effect Although it is generally believed that the beneficial effect of loop diuretics is the result of a rapid increase in diuresis, substantial evidence, from a large number of in vivo and in vitro experiments, has accumulated showing that administration of furosemide causes vascular effects, which probably contribute to its acute clinical effects

At first sight the reports on the vascular non-diuretic effects of furosemide seem conflicting However a great deal of the disparity in the results seem to be due to differences in the vascular bed studied (arterial or venous, renal or pulmonary, etc) the species studied, the timing (acute vs chronic effects), systemic vs local effects, direct vs indirect effects and differences in disease states In this paper the literature on vascular effects of loop diuretics (with emphasis on furosemide) is reviewed with reference to the differences in experimental protocols Finally some general conclusions are drawn and suggestions for future investigations are given

IN VITRO STUDIES

The direct vascular effects of furosemide are difficult to study in vivo because of interfering counteracting mechanisms which may even completely mask direct effects In a number of in vitro studies the presence of Na K 2Cl -cotransport activity has been demonstrated in endothelial as well as in vascular smooth muscle cells [1 3], and this observation represents a primary focus of interest with regard to the vascular effects of furosemide However, inhibition of Na K 2Cl -cotransport activity occurs only at high furosemide concentrations These concentrations are reached in the renal tubule, but not in the cardiovascular system [4] It should be emphasized that in all in vitro studies much higher concentrations were needed to induce vascular responses than in the human in vivo situation An additional difference causing much higher concentrations of free furosemide is the absence of protein binding in the media used

Table 1. *In vitro experiments on the vascular effects of furosemide*

Vasculature	Species	Drug-concentration	Main effects	Reference
Arterial				
Aorta	Rabbit	330 μg ml^{-1}	Hyperpolarisation and relaxation of smooth muscle cells	[6]
Mes	Rat	1-81 μg ml^{-1}	Dose-dependent inhibition of response to norepinephrine	[7]
Ear and renal	Rabbit	20 μg ml^{-1}	Inhibition of response to norepinephrine, attenuated by albumin	[8]
Ear	Rabbit	20-330 μg ml^{-1}	Direct endothelium independent relaxing effect	[9]
Pul, mes, tib	Dog	32-960 μg. ml^{-1}	No relaxation of precontracted arteries	[10]
Tail	Rat	5 mg kg^{-1}*	Endothelium-dependent reduction of electrical stimulated contraction	[11]
Venous				
Portal	Rat	1-100 μg. ml^{-1}	Reduction of response to norepinephrine and angiotensin II	[5]
Portal	Rabbit	20 μg ml^{-1}	Inhibition of response to norepinephrine, attenuated by albumin	[8]
Pulmonary	Dog	32-960 μg ml^{-1}	Endothelium-independent relaxation of norepinephrin-induced contraction	[10]

Abbreviations: Ear = central ear artery; Mes = mesenterial, Pul = pulmonary; Tib = anterior tibial artery
**Administered dose in stead of furosemide concentration*

The in vitro studies focussing on the vascular effects of furosemide are summarized in Table 1. In the early 1970's an inhibitory effect of furosemide on the vasoconstrictor response to norepinephrine and angiotensin II was observed in the rat portal vein [5]. It was demonstrated that incubation with furosemide causes a membrane hyperpolarisation of 5.5 mV in the relaxed rabbit pulmonary artery [6]. Many vasodilatory agents act by hyperpolarisation of the plasma membrane and subsequent closure of voltage dependent calcium channels, so this observation is consistent with, and possibly explains the direct vasodilatory action of furosemide.
Furosemide appeared to have a direct vascular effect in the perfused mesenteric vascular bed of the rat [7]. In an in vitro study with arterial vascular smooth muscle in segments of rabbit blood vessels, furosemide (20 mg. ml^{-1}) induced a small decrease in resting tension [8]. In the isolated rabbit central ear artery a direct relaxing effect of furosemide on isolated vessel segments was concentration-dependent (0.1-1.0 mM furosemide) [9]. It was demonstrated that inhibition of $Na^+K^+2Cl^-$ cotransport activity or hyperpolarization of the membrane was unlikely to be the sole mechanism responsible for the vasorelaxant effect of furosemide.
In an in vitro study using dogs it was demonstrated that furosemide did not have a direct effect on arterial smooth muscle, but exhibits selective venorelaxant activity [10]. The magnitude of this effect was most pronounced in the pulmonary vascular bed. Moreover, the vasorelaxant activity of furosemide was independent of endothelium, nitric oxide, cyclic GMP and prostanoids.
The role of the endothelium in the direct vascular effects of furosemide is still unclear. Whereas one report on an ex vivo experiment showed that the effect of furosemide on the response to sympathetic stimulation was endothelium-dependent [11], others did not find an important role for the endothelium in mediating the relaxation caused by furosemide in vitro [9]. The discrepancy between these results with respect to the endothelium-dependency may be caused by the different concentrations of furosemide studied and by the use of albumin-containing solutions [8].

Table 2 *In vivo experiments on the acute hemodynamic effects of furosemide*

Species (Diseases state)	Dose	Main effects	Reference
Human (AHF)	0 5-1 0 mg kg iv	Decrease PWP increase VC MAP and CO unchanged	[12]
Dog (ligated ureters)	2 mg kg	Decrease PWP PAP increase VC SVR MAP unchanged	[13]
Human (hypertension)	120-4000 mg day^{-1} po	Decrease MAP blood volume unchanged	[14]
Human (hypertension)	120-200 mg day^{-1} po	Decrease MAP and SVR increase VC blood volume unchanged	[15]
Human (hypertension)	80 mg iv	Decrease PAP and PWP and blood volume VC forearm unchanged	[16]
Human (CHF)	1 mg kg	Decrease PAP and CO	[17]
Human (CHF)	1 3 ±0 6 mg kg^{-1} iv	Decrease SVI increase MAP and SVR	[18]
Rat (hypertension)	3 mg kg iv	Decrease CO and SVI increase SVR	[19]
Human (salt depleted)	5-80 mg iv	Increase VC	[20]

Abbreviations AHF = acute heart failure, CHF = chronic heart failure, CO = cardiac output, iv = intravenously, MAP = mean arterial pressure, PAP = pulmonary arterial pressure, po = orally, PWP = pulmonary wedgepressure, SVI = stroke volume index, SVR = systemic vascular resistance, SVI – stroke volume index, VC = venous capacitance

In vivo studies after systemic administration

During the 1970's interest increased in the vascular effects of diuretics With the development of tools to monitor changes in hemodynamic parameters, these effects could be described more appropriately In most of these studies, as discussed in the next paragraph and summarized in Table 2 loop diuretics were administered systemically However, it should be noted that changes in hemodynamic parameters observed directly after administration of the loop diuretic, do not necessarily imply direct vasoactivity of the loop diuretic

A study by *Dikshit et al* is one of the first reports that focussed on the vascular effects of loop diuretics [12] In 20 patients with left ventricular failure, intravenous administration of furosemide caused a prompt fall in left ventricular filling pressure, which was accompanied by an increase in venous compliance, the latter being a marker for venodilatation These phenomena preceded an increase in urine and electrolyte output In dogs, furosemide produced a rapid reduction in pulmonary wedge pressure and an increase in venous compliance even though the ureters were ligated [13] These observations indicate that this venous effect may not have been the result of a decrease in plasma volume The dissociation of diuretic and vascular effects was confirmed in a study with hypertensive patients despite a fall in blood pressure, plasma volume did not change after administration of furosemide in combination with a high salt intake [14] In patients with peripheral oedema and mild hypertension the use of furosemide resulted in a decrease in mean arterial pressure, cardiac output and total peripheral resistance, whereas the venous capacitance increased without change in plasma and blood volume [15] However, the dissociation between venodilation and plasma volume is not always obvious In patients with mild heart disease or hypertension, 80 mg i v furosemide caused a decrease in right atrial pressure, pulmonary arterial pressure and pulmonary artery wedge pressure (signifying increased venous compliance), together with a decrease in cardiac index within 20 min [16] In this study, a hemoconcentration was observed as well, suggesting that the hemodynamic effects were secondary to intravenous volume reduction through diuresis The relationship between hemodynamic and hormonal changes after furosemide injection and during chronic furosemide treatment was studied in patients with congestive heart failure [17]

Cardiac output decreased significantly after furosemide injection (1 mg kg^{-1} body weight), reached its nadir after 90 min and returned to baseline within 4 h The mean pulmonary arterial pressure decreased steadily throughout the 4 h observation period These changes were not accompanied or preceded by changes in plasma renin activity, angiotensin II or aldosterone In this study patients were on a fixed diet, urine losses were not replaced isovolumetrically After continuous oral furosemide therapy during 8-10 days reciprocal changes between hemodynamic and hormone indices were observed As the diuretic response diminished, cardiac output and pulmonary arterial pressure declined, whereas the renin-angiotensin system was activated This suggests that during chronic therapy plasma renin activity and angiotensin II might counteract the vasodilatory effects of furosemide However, there are some reports that are in disagreement with this hypothesis [18,19] In patients with severe congestive heart failure, intravenously administered furosemide caused an early fall in stroke volume index and a quick transient increase in the systemic vascular resistance, a rise in mean arterial blood pressure (within 20 min after injection), associated with an increase in plasma renin activity, norepinephrine and plasma arginine vasopressin levels [18] These results were strengthened by the outcome of a study in spontaneously hypertensive rats [19], in which furosemide (3 mg kg^{-1}) caused an early fall in stroke volume and cardiac index A decrease in mean arterial blood pressure was observed after a delay of 2 to 4 h, which sustained for 6 to 8 h after injection Total peripheral vascular resistance increased substantially and returned to baseline range within 24 h The supposed mechanisms involved in the differences between the acute and chronic effects include an adaptation of baroreflex activity, a direct vasodilatory effect of diuretics, a decreased reactivity of the vascular system to pressor stimuli, a reduction of extracellular body fluid volume, and/or the production of endogeneous vasodilator substances mediated by furosemide

The dose dependency of the vascular effects of furosemide was characterized in healthy volunteers by using dosages ranging from 5 to 80 mg [20] Increases in venous capacitance were observed 5 min after i v administration of 5 and 10 mg furosemide Over the dose range 20 80 mg, no significant increases were observed However, after 10 min venous responses showed significant increases in venous capacitance, equally for all dosages used An oral dosage of 80 mg furosemide produced a rise in venous capacitance, 15 min after administration and a decrease in forearm bloodflow 15-60 min after administration A decrease in calf blood flow was observed within 15 min following administration of furosemide, regardless of salt balance or use of indomethacin [20] This latter effect of furosemide was associated with a rise in plasma renin activity and was not observed in anephric patients [21]

Table 3 *Experiments on the role of the kidney in the vascular effects of furosemide*

Species (Disease state)	Dose	Main effects	Reference
Human (Functionally anephric)	3 mg kg^{-1} iv	Increase FBF unchanged SBP VC weight hematocrit PRA	[21]
Human (anephric)	80 mg iv	VC and BP unchanged	[22]
Rat (acute nephrectomy)	5 mg kg^{-1} iv	Complete inhibition of vasoconstrictor response to NE and AT II	[23]
Dog (ligation ureters)	2 mg kg^{-1} iv	Decrease PAP and PWP increase SVR and VC BP unchanged	[13]
Dog (acute nephrectomy)	2 mg kg^{-1} iv	no hemodynamic changes	[13]

Abbreviations AT II = angiotensin II, BP = blood pressure, FBF = forearm blood flow iv = intravenously, NE = norepinephrin PAP = pulmonary arterial pressure, PRA = plasma renin activity, PWP = pulmonary wedge pressure, SBP = systolic blood pressure, SVR = systemic vascular resistance, VC = venous capacitance

THE ROLE OF KIDNEYS

In an attempt to elucidate the role of the kidneys in the hemodynamic effect of furosemide, vascular responses were studied in functionally anephric hypertensive patients [21] In contrast to experiments in subjects with normal renal function, intravenously administered furosemide caused a significant increase in forearm blood flow of 55% within 15 min, whereas venous capacitance weight hematocrit and plasma renin activity were unchanged (see Table 3) Possibly, this represents a direct vascular effect of furosemide, which becomes unmasked in the absence of counteracting mechanisms, such as the renin-angiotensin system In another study, the effect of intravenously administered furosemide on venous capacitance and calf blood flow was compared in healthy volunteers and anephric patients [22] Venous capacitance increased in healthy volunteers, but not in anephric patients Moreover, this effect of furosemide required a salt retaining state and it could be blocked by the use of the cyclo-oxygenase blocker indomethacin, suggesting an important role for renal prostaglandins in the systemic vascular effects of furosemide

Furosemide (5 mg kg^{-1}) attenuated the vasoconstrictor responses of the mesenteric blood vessels in the rat to both exogeneous angiotensin II and norepinephrine [23] Acute bilateral nephrectomy or treatment with indomethacin (2 mg kg^{-1} i v) completely prevented this inhibitory effect In a subsequent report the inhibitory effect of furosemide on the vasoconstrictor response to sympathetic nerve stimulation was absent after chemical renal medullectomy [24] The authors explained this effect by postulating that in the renal medulla non-prostanoid vasodilatory lipids are produced which mediate the vasodilatory effect of furosemide [25] Intrarenal prostaglandins probably are involved in the release of such a lipid Although substantial evidence of a direct vascular effect of furosemide is available from several in vitro experiments (see foregoing and Table 1), a coincidence of hormonal changes with the observed vascular effects was not considered

THE RENIN-ANGIOTENSIN-ALDESTERONE SYSTEM

The release of renin is controlled by three mechanisms the intrarenal baroreceptor, the sympathetic nervous system and the macula densa receptor [26] Results of some studies show a participation of prostaglandins in the renin release [27-29] It was demonstrated that prostaglandins mediate renin release in response to intrarenal baroreceptor stimulation [30] On the other hand, renin release due to symthathetic nerve stimulation is prostaglandin-independent [31]

Micropuncture experiments in rats indicate that renin release resulting from macula densa receptor stimulation during sodium deprivation is prostaglandin-dependent [29], whereas in dogs the macula densa mechanism of renin release could be blocked by inhibition of prostaglandin synthesis [32] It is known from ex vivo experiments that furosemide exerts a direct stimulating effect on renin secretion [33] In the isolated perfused rat kidney, furosemide-stimulated renin secretion did not require intact PGI synthesis [34] The authors proposed that increased prostaglandin production and increase of renin release after furosemide administration is not causally related, but may be based on a common response to changes in sodium balance In fact, prostaglandin synthesis could even be a counteracting mechanism participating in the vasoconstrictor action of angiotensin II [35]

The importance of angiotensin II in the vascular effects of 5 mg intravenously administered furosemide was studied in healthy volunteers [36] Captopril 50 mg abolished the acute increases in venous capacitance and attenuated the increase in forearm vascular resistance The mechanism suggested is that angiotensin II is formed secondarily to furosemide-stimulated renin release, and that the decrease in forearm blood flow is the result of the vasoconstrictive effect of angiotensin II Angiotensin II receptors are virtually absent in veins, so the net effect appears to be venodilation due to the angiotensin induced release of vasodilatory prostaglandins from the kidney [36] This view may not be entirely correct, as it has been demonstrated that angiotensin II has a direct venoconstrictive effect on the human dorsal hand vein [37]

To determine whether the vascular effects of furosemide are shared by bumetanide, another frequently used loop diuretic, the vascular and renal effects of equipotent dosages of furosemide and bumetanide were compared in healthy volunteers with moderate [38] and severe salt depletion [39] In the case of moderate salt depletion, both furosemide (10 and 100 mg) and bumetanide (250 μg and 250 mg) caused an increase in renal blood flow in both dosages Changes in peripheral vascular responses did not differ from placebo Both treatments led to an acute increase in urinary prostaglandin metabolite excretion (which may be a reflection of an increased renal blood flow) and plasma renin activity (the latter not increased by bumetanide 250 μg) Angiotensin II was increased significantly 30 min after 100 mg furosemide and 2 5 mg bumetanide Plasma norepinephrine was not influenced by any of the treatments [38] In contrast with these observations was the vascular response on furosemide (10 and 20 mg) and bumetanide (250 and 500 μg) in marked salt depletion [39] Significant reductions in forearm blood flow were observed after both furosemide dosages, but not after either of the bumetanide dosages Both drugs had no significant influence on venous capacitance Furosemide induced an increase in plasma renin activity, whereas bumetanide did not The differences between furosemide and bumetanide with regard to acute arterial vasoconstrictive activity may be attributed to the ability of furosemide (and the disability of bumetanide) to stimulate acute renin release from the kidney

The discrepancy between the results of this study [39] and the study *by Johnston et al* [38] with respect to vascular effects may be caused by differences in the degree of salt depletion This is emphasized by others [17,40] There are no in vitro studies that compare the vascular effects of furosemide and bumetanide As illustrated in the foregoing paragraphs, the total body sodium content is an important factor in the modulation of the indirect vascular response to furosemide Administration of a loop diuretic to a salt-depleted subject may further activate the renin-angiotensin system, causing a more pronounced arterial vasoconstriction

Prostaglandins

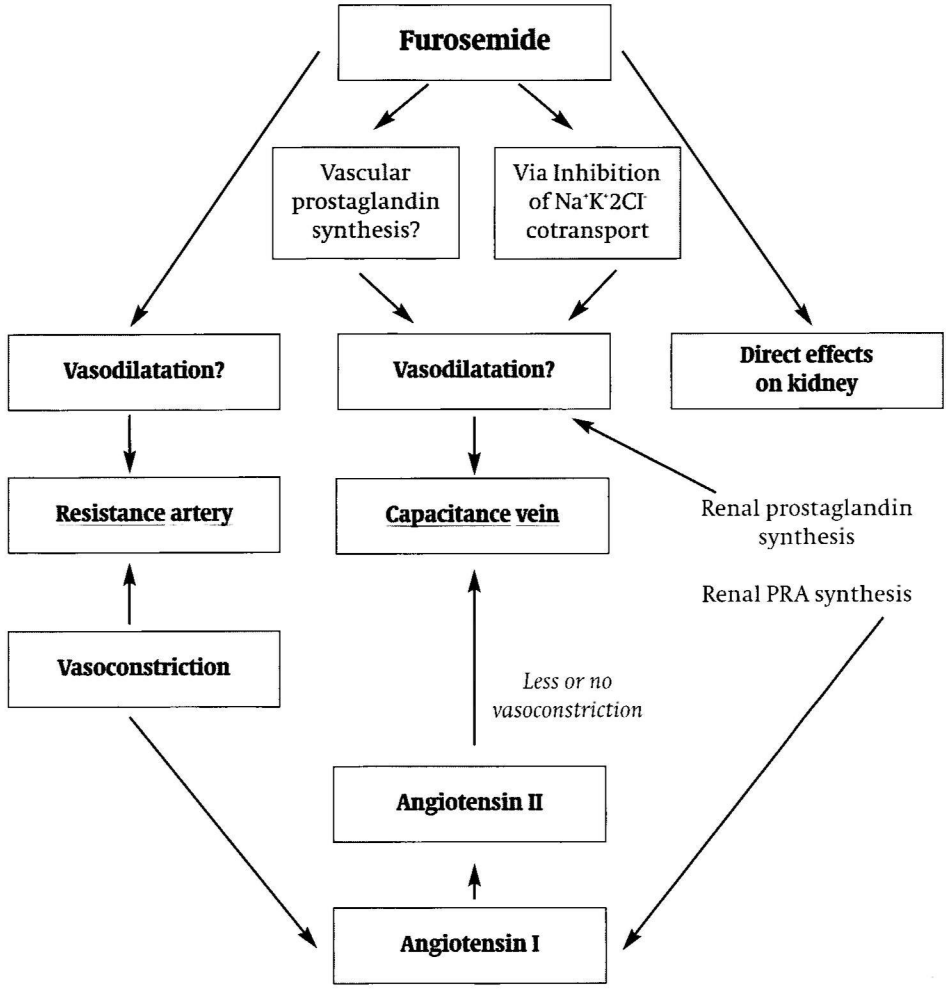
In 1975 it was shown in dogs that pretreatment with the cyclo-oxygenase inhibitor indomethacin blocked the increase in renal blood flow caused by furosemide [41] Since then several studies explored the role of prostaglandins in the natriuretic and vascular reponses to furosemide [30,34,40,42-52] It is of importance to distinguish the effects of circulating prostaglandins of renal origin from prostaglandins produced in the local (extrarenal) vascular bed, since the furosemide-induced vascular effects may well be dependent on prostaglandins locally produced in the vessel wall However, in in-vivo experiments it is difficult to study these two sources of prostaglandins separately

The kidney releases PGI , PGE , PGF, and tromboxane A, [42] PGI, and PGE_2 possess important vasodilatory properties under conditions of prior vasoconstriction Prostaglandin-induced vasodilatation plays an important role in the maintainance of glomerular filtration and perfusion by dilatation of the afferent arteriole in a salt deplete state, when the renin-angiotensin system is activated [53] Furosemide has been shown to increase the urinary excretion of prostaglandin [38,50,52] Whether this is caused by increased renal blood flow or by increased production of prostaglandins is unclear On the other hand, the reports on the effects of inhibition of prostaglandin synthesis on furosemide-induced natriuresis are conflicting, probably due to varying salt balances during the experiments [42]

In healthy volunteers PGI, induced renin release and furosemide-induced renin release was associated with renal PGI_2 formation [54] In a study performed in normotensive volunteers, indomethacin (75 mg) decreased both the peak urine flow rate and total sodium excretion within 1 h of a 30 mg i v furosemide dose, while an increase in renal plasma flow and glomerular filtration rate after furosemide was inhibited [48] The increase of urinary excretion of PGE, was abolished by indomethacin The urinary excretion of a metabolite of systemic PGI_2 was unaltered after furosemide injection The authors stated that the early hemodynamic effects of furosemide depend on an increased synthesis of prostaglandins, particularly PGE, and probably also PGI However, it is questionable whether the non-renal effects are a result of increased circulating prostaglandin levels [24,43] Arguments that underscore these doubts are prostaglandins are very labile, are rapidly metabolized and increased plasma levels of prostaglandins have never been measured after furosemide administration

Although the studies mentioned above suggest that furosemide induces an increment in renal prostaglandin production, they do not clarify whether systemic prostaglandin synthesis - the local production in the extrarenal vasculature - is increased by furosemide Mediation of the cardiovascular effects of furosemide by vascular products of the arachidonate metabolism were studied in ex vivo experiments, using an isolated perfused canine lung lobe [47] Furosemide decreased the mean pulmonary artery pressure This direct arterial vasodilatory activity of furosemide was similar to that of PGI and could be inhibited with indomethacin, suggesting that furosemide induces a local production of PGI, in resistance and/or capacitance vessels Recently, an in vitro study was published showing that furosemide in primary cultured bovine aortic endothelial cells stimulated the formation of endothelium derived kinin, a potent stimulator of endothelial nitric oxide and PGI formation [43] These experiments suggest that hemodynamic effects of furosemide are mediated by prostaglandins released from the local vasculature

Figure 1. *Diagrammatic scheme illustrating the possible mecanisms of furosimide-induced vascoactivity on artery and vein. The upper part of the figure represents direct vascular effects, whereas the lower part represents the vascular effects mediated by hormonal changes*



Conclusions

Although in the past 25 years much research has been done, the exact mechanism by which furosemide induces its vascular effects remains unclear. In Figure 1 the mechanisms involved in the vascular effects are shown. It seems clear that both direct and indirect mechanisms play a role. The venous vascular response to furosemide appears to be a direct effect, while the arterial response in vitro only occurs at supratherapeutic concentrations, and probably is mediated and modified by other factors like the degree of salt depletion, renin, angiotensin II and prostaglandins in vivo. The prostaglandins are either produced by the kidneys or by the endothelium, whereas the precise role of the endothelium has not yet been completely clarified.

Much attention has been paid to the arterial response, while the effects on the venous component have only been roughly monitored due to a lack of sensitive techniques to monitor local venous effects. However, especially in patients suffering from cardiac failure, the venous vasodilation might be of importance in the observed acute beneficial effects.

There are two methods available to study direct vascular effects in vivo. First, direct effects on resistance arteries in the human forearm can be studied with the perfused forearm technique. Using this method direct vasoconstrictive or vasodilator effects on resistance arteries in the human forearm can be examined by drug administration into the brachial artery and venous occlusion plethysmographic recordings [55]. Second, with a linear variable differential transducer it is possible to measure direct venous vascular effects on a selected dorsal hand vein [56,57]. With these methods it is possible to examine local vascular effects without provoking systemic counterregulatory effects. In a quest to explore the genuine direct vascular effects of loop diuretics in vivo, these methods provide the best options for future studies.

References

1 O'Donnell MF, Owen NE. Regulation of ion pumps and carriers in vascular smooth muscle. Physiol Rev 1994; 74: 683-721
2 O'Donnell ME, Owen NE. Sodium cotransport in vascular smooth muscle cells. Blood Vessels 1991; 28: 138-146
3 O'Donnell ME. [3H]bumetanide binding in vascular endothelial cells: Quantitation of Na-K-Cl cotransporters. J Biol Chem 1989; 264: 20326-20330
4 Flory JC, Stewart GW. The human erythrocyte Cl dependent Na-K cotransport system as a possible model for studying the action of loop diuretics. Br J Pharmacol 1982; 75: 183-188
5 Blair-West JR, McKinley MJ, McKenzie JS. Effect of frusemide on the reactivity of rat portal vein. J Pharm Pharmacol 1972; 24: 442-446
6 Kreye VA, Bauer PK, Villhauer I. Evidence for furosemide-sensitive active chloride transport in vascular smooth muscle. Eur J Pharmacol 1981; 73: 91-95
7 Handa M, Kondo K, Saruta T. Effects of diuretics on the vasoconstrictor responses to norepinephrine and potassium ions in the rat mesenteric artery. Arch Int Pharmacodyn Ther 1983; 262: 124-131
8 Andreasen I, Christensen JH. The effect of furosemide on vascular smooth muscle is influenced by plasma protein. Pharmacol Toxicol 1988; 63: 324-326
9 Ilan R, Aalkjaer C, Andreasen F. Mechanisms behind the relaxing effect of furosemide on the isolated rabbit ear artery. Pharmacol Toxicol 1991; 68: 406-410
10 Greenberg S, McGowan C, Xie J, Summer WR. Selective pulmonary and venous smooth muscle relaxation by furosemide: a comparison with morphine. J Pharmacol Exp Ther 1994; 270: 1077-1085
11 Gerkens JF. Inhibitory effect of furosemide on sympathetic vasoconstrictor responses: dependence on a renal hormone and the vascular endothelium. Clin Exp Pharmacol Physiol 1987; 14: 371-377
12 Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 1973; 288: 1087-1090
13 Bourland WA, Davy DK, Williamson HE. The role of the kidney in the early nondiuretic action of furosemide to reduce elevated left atrial pressure in the hypervolemic dog. J Pharmacol Exp Ther 1977; 202: 221-229
14 Cantarovich F, Benedetti F, Fernandez JC, et al. High doses of furosemide and sodium in hypertension. A single therapeutic measure in severe cases. Nephron 1974; 12: 133-139
15 Marchos AP, Magrini F. Hemodynamic effects of diuretics in patients with marked peripheral edema and mild hypertension. Clin Pharmacol Ther 1982; 31: 370-376
16 Hesse B, Nielsen J, Lund-Jacobsen H. The early effects of intravenous frusemide on central haemodynamics, venous tone and plasma renin activity. Clin Sci Mol Med 1975; 49: 551-555
17 Ikram H, Chan W, Espiner EA, Nicholls MG. Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. Clin Sci 1980; 59: 443-449
18 Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med 1985; 103: 1-6

19 Struyker Boudier HA Smits JF Kleinjans JC van Essen H Hemodynamic actions of diuretic agents Clin Exp Hypertens A 1983 5 209 223
20 Johnston GD Nicholls DP Leahey WJ The dose-response characteristics of the acute non-diuretic peripheral vascular effects of frusemide in normal subjects Br J Clin Pharmacol 1984 18 75 81
21 Mukherjee SK Katz MA Michael UF Ogden DA Mechanisms of hemodynamic actions of furosemide: differentiation of vascular and renal effects on blood pressure in functionally anephric hypertensive patients Am Heart J 1981 101 313 318
22 Johnston GD Hiatt WR Nies AS Payne NA Murphy RC Gerber JG Factors modifying the early nondiuretic vascular effects of furosemide in man: The possible role of renal prostaglandins Circ Res 1983 53 630 635
23 Gerkens JF Smith AJ Inhibition of vasoconstriction by frusemide in the rat Br J Pharmacol 1984 83 363 371
24 Gerkens JF Armsworth SJ Bhagwandeen SB Smith AJ Chemical renal medullectomy prevents frusemide-induced inhibition of sympathetic vasoconstriction in the in situ blood perfused rat mesenteryJ Hypertens 1987 5 273 275
25 Gerkens JF Armsworth SJ Dosen PJ Smith AJ Endothelium dependent inhibition of sympathetic vasoconstriction by frusemide administration to rats Clin Exp Pharmacol Physiol 1988 15 449-455
26 Davis JO Freeman RH Mechanisms regulating renin release Physiol Rev 1976 56 1 56
27 Oates JA Whorton AR Gerkens JF Branch RA Hollifield JW Frolich JC The participation of prostaglandins in the control of renin release Fed Proc 1979 38 72 74
28 Patrono C Pugliese F The involvement of arachidonic acid metabolism in the control of renin release J Endocrinol Invest 1980 3 193 201
29 Francisco LJ Osborn JL DiBona GF Prostaglandin in renin release during sodium deprivation Am J Physiol 1982 243 F537 F542
30 Data JL Rane A Gerkens J, Wilkinson GR Nies AS Branch RA The influence of indomethacin on the pharmacokinetics diuretic response and hemodynamics of furosemide in the dog J Pharmacol Exp Ther 1978 206 431 438
31 Kopp U, Autell M Sjolander M Ablad B The role of prostaglandins in the alpha- and beta-adrenoceptor mediated renin release response to graded renal nerve stimulation Pflugers Arch 1981 391 1 8
32 Gerber JG Nies AS Olsen RD Control of canine renin release: macula densa requires prostaglandin synthesis J Physiol 1981 319 419 429
33 He XR Greenberg SG Briggs JP Schnermann J Effects of furosemide and verapamil on the NaCl dependency of macula densa mediated renin secretion Hypertension 1995 26 137-142
34 Barden AE Mahonty DP Tunney AM Vandongen R Frusemide releases renin in the rat kidney when prostacyclin synthesis is suppressed Br J Pharmacol 1984 82 493 499
35 Packer M Interaction of prostaglandins and angiotensin II in the modulation of renal function in congestive heart failure Circulation 1988 77 164-173
36 Johnston GD Nicholls DP Leahey WJ Finch MB The effects of captopril on the acute vascular responses to frusemide in man Clin Sci 1983 65 359-363
37 Collier JG Robinson BF Comparison of effects of locally infused angiotensin I and II on hand veins and forearm arteries in man: evidence for converting enzyme activity in limb vessels Clin Sci Mol Med 1974 47 189 192
38 Passmore AP Whitehead EM Johnston GD Comparison of the acute renal and peripheral vascular responses to frusemide and bumetanide at low and high dose Br J Clin Pharmacol 1989 27 305 312
39 Johnston GD Nicholls DP Kondowe GB Finch MB Comparison of the acute vascular effects of frusemide and bumetanide Br J Clin Pharmacol 1986 21 359 364
40 Gerber JG Nies AS Furosemide-induced vasodilation: importance of the state of hydration and filtration Kidney Int 1980 18 454 459
41 Williamson HE Bourland WA Marchand GR Inhibition of furosemide-induced increase in renal blood flow by indomethacin Proc Soc Exp Biol Med 1975 148 164-167
42 Patrono C Dunn MJ The clinical significance of inhibition of renal prostaglandin synthesis Kidney Int 1987 32 1 12
43 Wiemer G Fink E Linz W Ilropot M Scholkens BF Wohlfart P Furosemide enhances the release of endothelial kinins nitric oxide and prostacyclin J Pharmacol Exp Ther 1994 271 1611 1615
44 Gerber JG Hubbard WC Branch RA Nies AS The lack of an effect of furosemide on uterine prostaglandin metabolism in vivo Prostaglandins 1978 15 663-670
45 Baille MD Crosslan K Hook JB Natriuretic effect of furosemide after inhibition of prostaglandin synthetase J Pharmacol Exp Ther 1976 199 469-476
46 Horrobin DF Manku MS Mtabaji JP Vascular actions of frusemide and bumetanide on the rat superior mesenteric vascular bed interactions with prostaglandins Clin Sci Mol Med Suppl 1976 3 257s 258s
47 Lundergan CF Fitzpatrick TM Rose JC Ramwell PW Kot PA Effect of cyclooxygenase inhibition on the pulmonary vasodilator response to furosemide J Pharmacol Exp Ther 1988 246 102 106
48 Mackay IG Muir AL Watson MI Contribution of prostaglandins to the systemic and renal vascular response to frusemide in normal man Br J Clin Pharmacol 1984 17 513 519
49 Mtabaji JP Manku MS Horrobin DF Vascular actions of furosemide and bumetanide on the rat superior mesenteric vascular bed interactions with prolactin and prostaglandins Can J Physiol Pharmacol 1976 54 357 366
50 Scheler B Weber PC Time-dependent changes in prostaglandin excretion in response to frusemide in man Clin Sci 1979 56 77 81
51 Sullivan JM Patrick DR Release of prostaglandin I2-like activity from the rat aorta: effect of captopril furosemide and sodium Prostaglandins 1981 22 575 585
52 Katayama S Attallah AA Stahl RA Bloch DI Lee JB Mechanism of furosemide-induced natriuresis by direct stimulation of renal prostaglandin E2 Am J Physiol 1984 247 F555 F561
53 Yared A Kon V Ichikawa I Mechanism of preservation of glomerular perfusion and filtration during acute extracellular fluid volume depletion: Importance of intrarenal vasopressin-prostaglandin interaction for protecting kidneys from constrictor action of vasopressin J Clin Invest 1985 75 1477-1487
54 Patrono C Pugliese F Ciabattoni G et al Evidence for a direct stimulatory effect of prostacyclin on renin release in man J Clin Invest 1982 69 231-239
55 Benjamin N Calvet A Collier J Robinson B Vallance P Webb D Measuring forearm blood flow and interpreting the responses to drugs and mediators Hypertension 1995 25 918-923
56 Aellig WH Clinical pharmacology physiology and pathophysiology of superficial veins—1 Br J Clin Pharmacol 1994 38 181 196
57 Aellig WH Clinical pharmacology physiology and pathophysiology of superficial veins—2 Br J Clin Pharmacol 1994 38 289-305

DIRECT VASCULAR EFFECTS OF FUROSEMIDE IN HUMANS

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ABSTRACT

Background: In humans, hemodynamic changes observed within minutes after systemic administration of furosemide are often referred to as direct vasoactivity However, these immediate changes do not per se imply a direct vascular effect We examined the genuine direct vascular effects of furosemide on the human forearm vascular bed and dorsal hand vein

Methods and Results: Forearm blood flow in response to infusion of increasing dosages of furosemide into the brachial artery was recorded by venous occlusion plethysmography Local plasma concentrations of furosemide reached a maximum of 234 ±40 μg ml during the highest infused dose, but did not significantly affect the ratio of flow in the infused/non-infused arms Venous distensibility of a dorsal hand vein was measured using a linear variable differential transformer During precontraction with norepinephrine, five increasing dosages of furosemide (1 to 100 μg min) were administered locally Additional experiments using local administration of indomethacin or N^G- monomethyl-L-arginine (L-NMMA), were carried out to determine whether effects were dependent on local prostaglandin or nitric oxide synthesis, respectively Also, the effects of systemic administration of furosemide were examined Local administration of furosemide led to a dose-dependent venorelaxation of 18 ±6% at the first to 72 ±16% at the last dose Indomethacin almost completely abolished furosemide-induced venorelaxation, whereas L-NMMA had no effect Systemic administration of furosemide resulted in a time-dependent increase of hand vein distensibility, reaching 45 ±11% after 8 minutes.

Conclusions: Furosemide does not exert any direct arterial vasoactivity in the human forearm, even at supratherapeutic concentrations In contrast, at concentrations estimated to be in the therapeutic range, we observed a dose-dependent direct venodilator effect on the dorsal hand vein to be mediated by local vascular prostaglandin synthesis

INTRODUCTION

The loop-active diuretic furosemide has been the standard treatment for heart failure for several decades Apart from its primary diuretic action, furosemide is also thought to have effects on the cardiovascular system In heart failure, systemic administration of a loop-active diuretic has been reported to relieve the symptoms of pulmonary oedema immediately, even before diuresis sets in [1,2] Although these effects are referred to as "direct" vascular effects, systemic administration of a drug does not permit distinction between a direct action on the vascular wall versus changes induced by cardiovascular reflexes or regulatory systems

It is well established that furosemide itself stimulates the release of renin, thereby increasing levels of angiotensin II [3-5] as well as of prostaglandins from the kidney [6] The effects on these two vasoactive hormonal systems have been associated with arterial vasoconstriction and venous vasodilation observed after systemic administration of the drug [3,4] Conversely, various in vitro experiments indicate that furosemide, sometimes at rather high concentrations, does exert a direct vasodilator effect on isolated arterial and venous vessels [7,8,9] In the in vivo situation, this furosemide-induced direct arterial vasodilation could be blunted by the vasoconstrictive effects of angiotensin II after systemic administration, and it is not clear whether the previously reported in vivo venodilation is the result of a direct or indirect effect of furosemide on venous smooth muscle cells [1,3,10] Thus, up to now it is unknown whether furosemide-induced effects on systemic hemodynamics are the result of a direct or indirect action of the drug on the vasculature in vivo

In the present study, we thoroughly investigated the genuine direct vascular effects of furosemide on resistance arteries in the forearm and on the dorsal hand vein of healthy subjects To this end, we used the perfused forearm technique and the linear variable differential transformer (LVDT) technique, respectively With these methods interpretation of the results will not be confounded by direct effects on kidney or reflex effects secondary to changes in blood pressure or total plasma volume

METHODS

Subjects

Several protocols using two techniques were conducted for this study, all approved by the local ethics committee Before participation, written informed consent was obtained from a total of 60 healthy volunteers Participants were asked to refrain from drinking alcohol or caffeine containing beverages for at least 24 hours before their studies Salt intake was not restricted None of the participants smoked or used any medication (including analgesics) All experiments were performed in a single-blind fashion in a temperature-controlled laboratory (23°C to 24°C for the perfused forearm experiments and 28°C to 29°C for the venous distensibility measurements) with the subject in supine position

Demographic characteristics of the participants are summarized in Table 1

Table 1 *Demographic characteristics of the study groups*

	Arterial Vasoactivity	Venous Vasoactivity
n (M/F)	22 (21/1)	38 (33/5)
Age (years)	25 9 ±1 2	47 0 ±19 1
Weight (kg)	77 3 ±1 4	75 0 ±6 8
Height (cm)	183 ±2	182 ±6
Body mass index (kg m^{-2})	23 0 ±0 4	22 7 ±2 0
Syst blood pressure (mm Hg)	128 ±3	134 ±22
Diast blood pressure (mm Hg)	73 ±1	80 ±9

Data are mean ±SD

Arterial vascular activity measurements

Two protocols were conducted in a total of 22 subjects to assess the direct arterial vasoactivity of loop-active diuretics First, we examined the direct arterial vasoactivity of furosemide and bumetanide and second, the effect of locally administered furosemide on norepinephrine-induced vasoconstriction The perfused forearm technique was used for both protocols For this technique, the left brachial artery was cannulated with a 20-gauge catheter (Angiocath, Deseret Medical, Becton Dickinson) after induction of local anesthesia (lidocaine 2%) This catheter was used for drug infusion (automatic syringe infusion pump, type STC-521, Terumo) and blood pressure monitoring (Hewlett Packard GmbH) At least 30 minutes after intra-arterial cannulation, baseline values of FBF were measured in both arms three times per minute by ECG-triggered venous occlusion plethysmography with mercury-in-Silastic strain gauges (Hokanson EC4, DE Hokanson) [11]
To ensure that forearm bloodf low (FBF) recordings referred predominantly to the forearm skeletal muscle resistance arteries, the hand circulation was occluded during all FBF recordings by a wrist cuff inflated 100 mmHg above the systolic pressure [12] The upper arm collecting cuffs were simultaneously inflated to 45 to 50 mmHg with a rapid cuff inflator (Hokanson E-20) In all experiments, we also inserted a catheter into a deep ipsilateral forearm vein During the last minute of each drug infusion period of 10 minutes a venous blood sample was taken and drug concentrations were measured by high-performance liquid chromatography assay as previously described [13]

Direct arterial vasoactivity of loop-active diuretics

Dosages of furosemide were normalized to forearm volume (water displacement method) Total infusion rate was kept constant at 100 µl min^{-1} 100 ml of forearm volume^{-1} Furosemide was infused at 1-3-10-30-100 µg min^{-1} dl^{-1} in 8 subjects In another 6 subjects, furosemide was infused at 1000 µg min^{-1} dl^{-1} for 6 minutes In 4 subjects, we administered bumetanide (0 025-0 075-0 25-0 75-2 5 µg min^{-1} dl^{-1}) instead of furosemide to perceive possible differences in vasoactivity between these two loop-active diuretics

Effect of furosemide on norepinephrine-induced vasoconstriction

Animal data suggest that furosemide may exert an anti vasoconstrictor effect, because the drug did not directly dilate mesenteric resistance vessels but rather inhibited the vasoconstrictor effect of norepinephrine and angiotensin II [14] To study this possible mechanism in humans, we measured the reduction of FBF in response to cumulative intra-arterial norepinephrine infusions in the absence and presence of local furosemide administration

In 4 subjects, norepinephrine was infused at 10, 30, and 100 ng min^{-1} dl^{-1} before and after local administration of furosemide (10 µg min^{-1} dl^{-1} for 20 minutes, preceded by a 30-minute interval after the first norepinephrine dose-response curve). Previous experiments revealed that intrabrachial infusion of this dose of furosemide led to clinically relevant concentrations in the infused forearm.

Venous vascular activity measurements

Four protocols were carried out to determine the venous vasoactivity of furosemide. The direct venous effect of locally administered furosemide was examined, after which involvement of vascular prostaglandin and nitric oxide (NO) synthesis was assessed. Also, the venous effect of systemic administration of furosemide was examined. All protocols were conducted by the LVDT technique, in which venous distensibility of a dorsal hand vein was measured with LVDT as described by *Aellig* [15] and evaluated by *Alradi and Cairuthers* [16]. A total of 51 experiments were performed in 28 young and 10 elderly subjects. Regression analysis established that there was no significant correlation between age and percentage venodilation (r=0.18, p=NS), after which all data were pooled. With the subject in the supine position in a temperature controlled laboratory (28°C to 29°C), the arm under investigation was placed on a rigid support at an angle of 30° from the horizontal to allow complete emptying of the superficial hand veins. A sphygmomanometer cuff placed on the upper arm was then inflated to 45 mmHg. A suitable large superficial vein with no apparant tributaries in the immediate area of examination was chosen, and a 23-gauge butterfly needle was inserted into the vein. The lightweight (0.2-g) probe of the LVDT was placed over the summit of the chosen vein 10 mm downstream from the tip of the needle. Under these conditions, dorsal hand vein distensibility is maximal during venous occlusion. When the venous pressure remains constant at 45 mmHg, changes in venous diameter are proportional to changes in venous tone.

Owing to the low venous tone present under these conditions [17], venodilator effects can only be quantified on veins that have been preconstricted. To examine furosemide-induced venodilation, we used continuous infusion of increasing concentrations of norepinephrine to precontract the veins. Infusion of the norepinephrine concentration that achieved a precontraction of ≈30% of maximal vein diameter was sustained throughout the experiment. Previous experiments from our laboratory showed that this method has a good reproducibility. In 15 subjects the coefficient of variation of the maximal vasoconstrictor response to norepinephrine (before and after an interval of 2 hours) was 9%. In addition, norepinephrine dose-response curves on different days did not significantly differ from each other. Sustained infusion of norepinephrine alone resulted in a stable vasoconstrictor response (70 ±7% contraction after 10 min and 73 ±6% contraction after 60 min, n=10), indicating the absence of tachyphylaxis to norepinephrine. During the experiment blood pressure and heart rate were monitored every 5 minutes by a Dinamap 1846 SX attached to the contralateral arm.

Direct venous vasoactivity of furosemide

In a total of 20 subjects, NaCl 0.9% (0.1 ml min^{-1}) was replaced by five increasing doses of furosemide (1, 3, 10, 30, and 100 µg min^{-1}) at the same infusion rate for 10 minutes each. The cuff was deflated for 30 seconds every 5 minutes. At the end of the experiment, saline was infused again, still with concomitant norepinephrine infusion.

Involvement of vascular prostaglandin synthesis in the direct venous vasoactivity of furosemide

In vivo, an increase in the venous capacitance induced by systemically administered furosemide has been reported to be inhibitable by indomethacin [3]. This observation suggests a role for prostaglandins as a mediator of vasoactive effects of furosemide. The source of the prostaglandins involved in this mechanism may be the kidneys, because they may release prostaglandins into the systemic circulation [3], alternatively, local production in the peripheral vasculature could be involved [18]. To determine the role of the nonrenal prostaglandins in the venous vasoactive effects of furosemide, we examined the effect of locally administered indomethacin (12.5 μg · min⁻¹, 10 minutes) on the furosemide-induced venous vasoactivity. In 8 subjects furosemide (100 μg · min⁻¹) together with a placebo (NaCl 0.9%, 0.1 ml · min⁻¹) was locally infused into a preconstricted vein for 10 minutes. Venodilation was assessed, after which placebo was replaced by indome-thacin for 10 minutes and venodilation was assessed again. To exclude a possible constrictor response by indomethacin alone, control experiments were performed in 4 subjects to determine the effect of indomethacin (12.5 and 125 μg · min⁻¹) on baseline venous tone.

Involvement of vascular NO synthesis in the direct venous vasoactivity of furosemide

NO is a potent vasodilator released by vascular endothelial cells. Although the furosemide-induced vascular effects in vitro appear to be independent of the endothelium, a recent study showed that furosemide augmented the NO production of isolated cultured endothelial cells [7,18]. To study the role of NO in the furosemide induced venous vasoactivity, we repeated the protocol as described above, now using N^{ω}-monomethyl-L-arginine (L-NMMA) (60 μg · min⁻¹) instead of indomethacin to inhibit NO production. Extensive studies have shown that this dose of L-NMMA has no effect on basal venous tone and is able to block the venodilation caused by acetylcholine [19,20].

Effect of systemic administration of furosemide on dorsal hand vein distensibility

All previous reports concerning the effects of furosemide on human vein capacitance used systemic administration [1,3,4,10]. To examine whether furosemide administered systemically in therapeutic dosages exerts a vasodilator activity comparable to that of locally administered furosemide, we administered furosemide (40 mg) intravenously in the contralateral arm in 15 subjects. Venous distensibility of the precontracted hand vein was recorded during the following 8 minutes.

Drugs

Furosemide solutions were freshly prepared from 2-ml ampoules containing 10 mg · ml⁻¹ furosemide as a disodium salt (Lasix, Hoechst Marion Roussel) and were further diluted in physiological saline immediately before each experiment. Norepinephrine (1-mg · ml⁻¹ ampoules), indomethacin (Indocid PDA, Merck Sharp and Dome, 1-mg · ml⁻¹) and L-NMMA acetate (Clinalfa) were dissolved in physiological saline immediately before use.

Data analysis

Data are expressed as mean ±SEM unless noted otherwise and were analyzed by Student's *t* test or repeated measures ANOVA for paired data if appropiate. If ANOVA showed that a significant difference existed between conditions, it was followed by post hoc *t* tests (including Bonferroni correction) to determine dose dependency or time dependency. Linear regression analysis was performed on the relation between age and percentage furosemide-induced venodilation (correlation coefficient according to Pearson). A value of $p<0.05$ was considered to indicate significance.

Direct arterial vasoactivity
To reduce the variability of blood flow data and to correct for systemic changes, the ratio of the FBF measurements in the infused and noninfused arm was calculated for each time point with the noninfused arm used as a contemporaneous control for the infused arm [21] The FBF values of the last 3 minutes of each drug infusion were averaged to one value
Direct venous vasoactivity
The response of norepinephrine-induced constriction was measured and furosemide-induced effects were expressed as the percentage attenuation of the average control constriction All results are expressed as a percentage of baseline vein size The furosemide-induced venodilation was determined during the last 3 minutes of each furosemide infusion

RESULTS

Systemic effects

Forearm volume averaged 984 ±32 ml During the arterial vasoactivity experiments, blood pressure, heart rate, and FBF in the noninfused arm did not change significantly after intra brachial infusion of furosemide During local administration of furosemide in the venous vasoactivity experiments, blood pressure increased over ≈1 hour from 113 ±2/62 ±1 to 116 ±2/66 ±2 mm Hg (for systolic and diastolic blood pressure p=0 03 and 0 003, respectively, ANOVA with repeated measures) There was no change in heart rate (61 ±2 to 61 ±2 bpm, p=NS) More relevantly, blood pressure increased within 5 minutes after systemic administration of 40 mg of furosemide from 118 ±1/68 ±2 to 121 ±2/71 ±2 mm Hg (p=0 01 and p< 0 0001, respectively, Student t test) Heart rate remained unchanged (63 ±2 to 65 ±1 bpm)

Direct effects on FBF

Ratios of infused to control FBF and ipsilateral venous plasma concentrations of furosemide are shown in Figure 1(top) During five increasing dosages of furosemide, there was no significant effect on FBF compared with the placebo infusion In 6 subjects, we infused furosemide 1000 µg min dl for 6 minutes, leading to local furosemide plasma concentrations of 234 ±40 µg ml In these subjects, furosemide increased FBF in the infused arm slightly, by 23 ±9 7% (p<0 05), but without a significant effect on the FBF ratio of the infused and noninfused arms (p=0 08)
Intra arterial bumetanide infusions led to local plasma concentrations ranging from 39 ±11 to 1748 ±327 ng ml and also failed to alter FBF (data not shown)

Effect of furosemide on norepinephrine induced vasoconstriction
As shown in Figure 1, local infusion of norepinephrine into the brachial artery led to a dose dependent decrease in FBF (p<0 001), with no significant effect on systemic blood pressure This vasoconstriction was not inhibited by local infusion of furosemide (p=NS)

Direct effects on dorsal hand vein distensibility

Vein diameter of the participants was 0 74 ±0 05 mm On average, infusion of norepinephrine constricted the vein of investigation to 31 ±2% of the control size

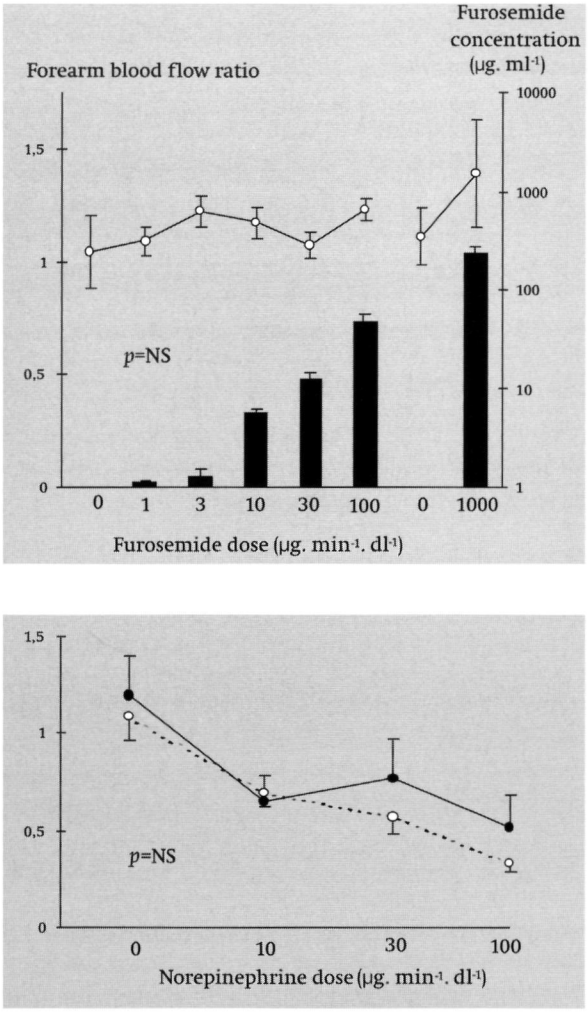

Figure 1. *Direct arterial vasoactivity of furosemide*

Top, bars represent mean ±SEM measured local venous plasma concentrations of furosemide (right axis). Line graph shows the mean ±SEM FBF ratio (infused/noninfused arm) during intrabrachial infusions of furosemide (left axis) as measured by venous occlusion plethysmography. There was no significant change in forearm blood flow ratio. Values are presented as mean ±SEM of 8 and 6 experiments

Bottom, ratio of FBF during intrabrachial norepinephrine administration, both in the presence of placebo (solid circles/solid line) and after and during concomitant infusion of furosemide (10 μg. min-1. dl-1, open circles/dashed line). Constrictor response to norepinephrine ($p<0.001$) was not inhibited by local furosemide administration (p=NS). Values are presented as mean ±SEM of 4 experiments. P values refer to statistical differences between conditions for these dose-responses as analyzed by ANOVA with repeated measures over the complete dose-response curves

Figure 2 demonstrates that continuous local infusion of furosemide results in a dose-dependent attenuation of the constrictor effect of norepinephrine ($p<0.001$). Post hoc t tests (with Bonferroni correction) revealed a dose-dependent venodilation between doses of 0, 1, 10, and 100 μg. min^{-1}. This direct venodilating effect of furosemide was rapid in onset. After the last furosemide infusion was replaced with NaCl 0.9% infusion, venodilation waned within a few minutes.

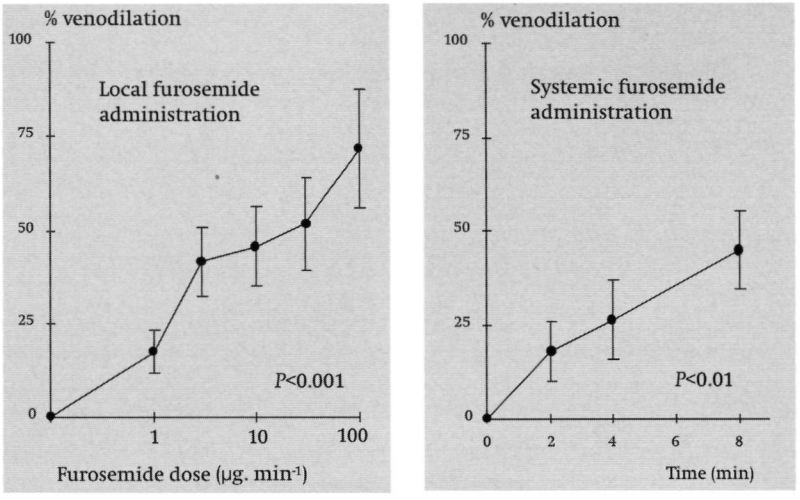

Figure 2. *Direct venous vasoactivity of furosemide*
Left, percentage increase in venous distensibility of a norepinephrine-constricted dorsal hand vein before and during increasing doses of local furosemide infusions. Values are presented as mean ±SEM of 20 experiments. Horizontal axis indicates dose infused per minute, not final concentration
Right, percentage increase in venous distensibility of a norepinephrine-constricted dorsal hand vein following contralateral systemic administration of furosemide (40 mg) at 2, 4 and 8 minutes after bolus injection. Values are mean ±SEM of 15 experiments. P values refer to the statistical differences between conditions for these dose- or time-dependent responses as analyzed by ANOVA with repeated measures over complete dose-response curves

Involvement of vascular prostaglandin synthesis in the direct venous vasoactivity of furosemide
In 8 subjects, furosemide-induced venorelaxation was assessed in the absence and presence of local indomethacin administration. Figure 3 (left) shows that indomethacin inhibits furosemide-induced venodilation, because in this sub-group furosemide dilated the vein by 54 ±17% and furosemide in combination with indomethacin, by 14 ±17% (p=0.025). Control experiments showed that indomethacin itself had no constrictor effect on basal vein tone. When baseline vein distensibility is taken as 100%, indomethacin 12.5 and 125 μg. min^{-1} led to vein distensibilties of 101.4 ±0.5% and 100.2 ±1.2%, respectively (n=4, p=NS).

Involvement of vascular NO synthesis in the direct venous vasoactivity of furosemide
Figure 3 (right) shows that furosemide-induced venorelaxation was not inhibited by local L-NMMA administration. In this subgroup, venorelaxation was 60 ±11% before and 53 ±14% after placebo was replaced by L-NMMA (n=8, p=NS).

Effect of systemic administration of furosemide on dorsal hand vein distensibility
As shown in Figure 2 (right), parenteral administration (contralateral antecubital vein) of 40 mg furosemide led to increases in vein diameter of 18 ±8%, 26 ±11% and 45 ±11% at 2, 4 and 8 minutes, respectively (p<0.01). Post hoc tests (Bonferroni) revealed that venodilation was significant from baseline at t=4 minutes (p=0.028) and 8 minutes (p=0.001).

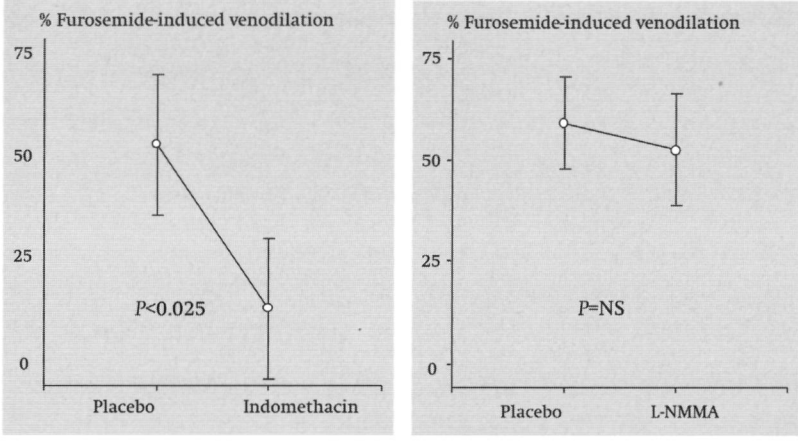

Figure 3. *Percentage increase in venous distensibility of a norepinephrine-constricted dorsal hand vein induced by local administration of furosemide (100 μg. min^{-1}) both in the presence of placebo and after and during concomitant infusion of indomethacin (12.5 mg. min^{-1}, left; p<0.025) or L-NMMA (60 mg. min^{-1}, right; p=NS). Values are mean ±SEM of 8+8 experiments. P values refer to statistical differences between conditions as analyzed by Student's t test for paired data*

Discussion

It is generally accepted that the reduction in venous return as a result of a nondiuretic vascular effect by furosemide is therapeutically important in achieving rapid symptomatic relief for patients with left ventricular heart failure. The mechanism of this action is unclear. Because of the absence of data on the direct vasoactivity of furosemide in vivo, we examined the vascular effects of local furosemide administration on arterial and venous vessels in humans. Our data strongly suggest that furosemide does not exert any direct arterial vasodilator or antivasoconstrictor activity in the human forearm but does have a direct venodilator effect, which is associated with vascular prostaglandin synthesis.

Direct effects on FBF

Our results demonstrate the absence of a direct effect of loop-active diuretics on FBF during intra-arterial infusions, which result in clinically relevant plasma concentrations in the infused forearm. The absence of vasoactivity in this concentration range is consistent with most previous experiments on isolated arteries [7,8]. In these in vitro experiments, direct vasodilator properties of furosemide were observed only at concentrations >10^{-4} mol.l^{-1}, whereas in our first series of experiments, the furosemide concentration at the highest infusion rate reached 47 ±10 mg. ml^{-1}, equivalent to $1.4^{*}10^{-4}$ mol. l^{-1}.

To examine the direct arterial effects of furosemide at very high concentrations in vivo, we infused furosemide 1000 mg min^{-1} dl^{-1} into the brachial artery, leading to a local concentrations of 234 ±40 μg ml^{-1} ($0.71 \cdot 10^{-3}$ mol l^{-1}). Even at these supratherapeutic concentrations, only a negligible increase in FBF was observed.

In the rat, furosemide did not change baseline mesenteric blood flow, but systemic administration did inhibit the decrease in blood flow produced by angiotensin II and norepinephrine [14]. In contrast, we observed no effect of local furosemide on norepinephrine-induced attenuation of FBF. From our studies, we conclude that furosemide does not exert any direct arterial vasodilator or antivasoconstrictor activity in the human forearm. As such, the previously reported decrease in forearm blood flow after systemic administration of furosemide is probably due to an indirect effect of the drug, in particular a stimulation of the renin-angiotensin system [3,4,22,5]. Of course, our experiments do not allow us to exclude direct arterial vasoactivity of furosemide in other vascular beds, eg, the lung or kidney.

Direct effects on dorsal hand vein distensibility

The present investigation shows that furosemide exerts a direct vasodilator effect on preconstricted dorsal hand veins. Time-control experiments demonstrated that this effect of furosemide cannot be explained by a spontaneous reduction in norepinephrine-induced constriction over time. The local concentration of furosemide cannot be estimated precisely because the venous flow was not measured in these studies. However, if the flow in the dorsal hand vein is assumed to be 1 ml min^{-1} (5% of arterial FBF) furosemide plasma concentrations can be estimated to range from 0.2 to 20 μg ml^{-1} during our dose-response studies [23]. Systemic administration of 40 mg furosemide leads to a plasma concentration of 3.8 ±0.3 μg ml^{-1} in the first 15 min in normal subjects, which is within the range of the estimated plasma concentrations [24]. This, as well as the observation of a similar venodilator effect after systemic administration of 40 mg of furosemide, suggests that the increase of venous compliance observed after systemic administration of furosemide may be the result of direct effects on the venous circulation. Compared to other substances such as nitroprusside and substance P, which exert venodilatory properties at an infusion rate of nanograms per minute, furosemide is much less potent [25,26]. However, its effect does have clinical relevance, especially in the first few minutes after parenteral administration.

Mechanism of action

Two hypotheses concerning the direct vascular effects of furosemide emerge from the literature. The first hypothesis focuses on furosemide-induced inhibition of vascular Na-K-2Cl cotransport, whereas the second is directed to the role of prostaglandins in the vascular activity of furosemide.

Na^+-K^+-2 Cl Cotransport Inhibition

The presence of Na-K-2Cl cotransport in endothelial and vascular smooth muscle cells has been established, but its role in regulation of vascular tone is unclear [27-29]. In a recent report, furosemide relaxed canine venous but not arterial vessels taken from a variety of vascular beds [9]. In the same vessels Na-K-2Cl cotransport distribution was determined and the magnitude of the vasodilator effect was found to correlate with Na-K-2Cl cotransport distribution. The correlation between Na-K-2Cl cotransport distribution and vascular activity suggests a role for this cotransporter in the vascular action of furosemide. However, inhibition of renal Na-K-2Cl cotransport occurs at 10^{-4}-10^{-3} mol l^{-1} furosemide [30], concentrations 10 to 50 times the local concentration in the hand vein, and the importance of this action of furosemide to its venodilator properties remains uncertain.

Augmented prostaglandin synthesis

The effect of systemic administration of furosemide on venous capacitance has been compared between healthy subjects and anephric patients Venous capacitance increased in healthy volunteers but not in anephric patients [3] This effect could be blocked by pretreatment of the cyclooxygenase inhibitor indomethacin, suggesting a role for renal prostaglandin release in the vascular effects of furosemide Our results indicate that renal prostaglandin synthesis is not necessarily important for the direct venous vasodilation, because the release of renal prostaglandins cannot have been stimulated after the local furosemide infusions This does not rule out the possibility that furosemide-induced vasodilation is mediated by activation of vascular PGI synthesis *Lundergan et al* , using an isolated canine lung lobe perfused with autologous blood at constant flow, demonstrated that furosemide-induced decreases in pulmonary artery perfusion pressure were mediated by prostaglandins because they were abolished by treatment of the lung with indomethacin [31] Recently, it was shown in cultured bovine aortic endothelial cells that furosemide stimulated the production of prostacyclin and NO at clinically relevant concentrations [18]

In our study, the direct venodilator effect of furosemide on veins was almost totally abolished by local administration of indomethacin, indicating that this direct vascular effect is dependent on local vascular prostaglandin synthesis It is unclear whether the endothelial or the vascular smooth muscle cell is the source of the prostaglandin production augmented by furosemide In vivo endothelial stripping with distilled water [32] seems a possibility to address this question, but these experiments are quite invasive and NSAID treatment will be necessary to prevent blood clotting [32], which will obscure the interpretation of the furosemide induced venodilation It is unknown whether the furosemide-enhanced vascular PGI, production [18] is the consequence of a nonspecific action of furosemide or due to inhibition of the vascular Na K -2Cl cotransporter Furthermore, the effect of systemic treatment with indomethacin or other NSAID's on the furosemide-induced venorelaxation and its clinical implications are unknown The venorelaxation persisted after addition of L-NMMA, so it appears that the effect is not mediated by endothelial nitric oxide release

Conclusions

The present study provides the first evidence that furosemide at therapeutic concentrations exerts no direct vasodilator or antivasoconstrictor effect on arterial resistance vessels in the human forearm but directly dilates veins in human The direct venodilation was inhibited by local indomethacin administration but not by blockade of NO synthesis, indicating that the direct vascular venodilation is dependent on local prostaglandin but not on NO production Hemodynamic changes observed directly after systemic administration of furosemide are probably due to a direct venodilator effect of the drug

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References

1 Dikshit K Vyden JK Forrester JS Chatterjee K Prakash R Swan HJ Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction N Engl J Med 1973 288 1087 1090
2 Bhatia ML Singh I Manchanda SC Khanna PK Roy SB Effect of frusemide on pulmonary blood volume Br Med J 1969 31 551-552
3 Johnston GD Hiatt WR Nies AS Payne NA Murphy RC Gerber JG Factors modifying the early nondiuretic vascular effects of furosemide in man The possible role of renal prostaglandins Circ Res 1983 53 630-635
4 Johnston GD Nicholls DP Teahey WJ Finch MB The effects of captopril on the acute vascular responses to frusemide in man Clin Sci 1983 65 359-363
5 Hesse B Nielsen I Unimpeded plasma renin increase after intravenous furosemide during saline replacement Scand J Clin Lab Invest 1976 36 23 28
6 Ciabattoni G Pugliese I Cinotti GA Strati G Ronci R, Castrucci G Pierucci A, Patrono C Characterization of furosemide induced activation of the renal prostaglandin system Eur J Pharmacol 1979,60 181 187
7 Tian R Aalkjær C Andreasen I Mechanisms behind the relaxing effect of furosemide on the isolated rabbit ear artery Pharmacol Toxicol 1991 68 406-410
8 Barthelmebs M Stephan D Fontaine C Grima M Imbs JL Vascular effects of loop diuretics an in vivo and in vitro study in the rat Naunyn-Schmiedeberg s Arch Pharmacol 1994 349 209-216
9 Greenberg S McGowan C Xie J Summer WR Selective pulmonary and venous smooth muscle relaxation by furosemide a comparison with morphine J Pharmacol Exp Ther 1994 270 1077 1085
10 Verma SP Silke B Hussain M Nelson GI Reynolds GW Richmond A Taylor SH First-line treatment of left ventricular failure complicating acute myocardial infarction a randomised evaluation of immediate effects of diuretic venodilator arteriodilator and positive inotropic drugs on left ventricular function J Cardiovasc Pharmacol 1987 10 38 46
11 Whitney RJ The measurement of volume changes in human limbs J Physiol Camb 1953 121 1 27
12 Tenders J Janssen GJ Smits P Thien T Role of the wrist cuff in forearm plethysmography Clin Sci 1991 80 413 417
13 Russel FGM Tan Y Mevel v in JJM Gribnau FWJ Ginneken van C AM Solid phase extraction of furosemide from plasma and urine and subsequent analysis by high-performance liquid chromatography J Chromat 1989 496 234-241
14 Gerkens JF Smith AJ Inhibition of vasoconstriction by frusemide in the rat Br J Pharmacol 1984 83 363 371
15 Aellig WH Methods for studying drug effects on superficial human veins Methods Find Exp Clin Pharmacol 1985 7 321 324
16 Alradi AO Cartuthers SG Evaluation and application of the linear variable differential transformer technique for the assessment of human dorsal hand vein alpha-receptor activity Clin Pharmacol Ther 1985 38 495 502
17 Collier JG Nachev C Robinson BF Effect of catecholamines and other vasoactive substances on superficial hand veins in man Clin Sci 1972 43 455-467
18 Wiemer G Fink L Linz W Ihropot M Scholkens BF Wohlfart P Furosemide enhances the release of endothelial kinins nitric oxide and prostacyclin J Pharmacol Exp Ther 1994 271 1611-1615
19 Collier J Vallance P L-NMMA increases arteriolar but not venous tone in humans the mechanism appears to be dependent of sympathetic tone J Cardiovasc Pharmacol 1991 17 S182 S185
20 Vallance P Collier J Moncada S Nitric oxide synthesised from L arginine mediates endothelium dependent dilatation in human veins in vivo Cardiovasc Res 1989 23 1053-1057
21 Greenfield ADM Patterson GC Reactions of blood vessels of the human forearm to increases in transmural pressure J Physiol Lond 1954 125 508 524
22 Johnston GD Nicholls DP Teahey WJ The dose response characteristics of the acute non-diuretic peripheral vascular effects of frusemide in normal subjects Br J Clin Pharmacol 1984,18 75-81
23 Robinson BF Collier JG Dobbs RJ Comparative dilator effect of verapamil and sodium nitroprusside in forearm arterial bed and dorsal hand veins in man functional differences between vascular smooth muscle in arterioles and veins Cardiovasc Res 1979 13 16 21
24 van Mevel JJM Smits P Russel FGM Gerlag PGG Tan Y, Gribnau FWJ Diuretic efficiency of furosemide during continuous administration versus bolus injection in healthy volunteers Clin Pharmacol Ther 1992 51 440 444
25 Collier JG Lorge RE Robinson BF Comparison of effects of tolmesoxide (RX71107) diazoxide hydrallazine prazosin glyceryl trinitrate and sodium nitroprusside on forearm arteries and dorsal hand veins of man Br J clin Pharmacol 1978 5 35 44
26 Strobel WM Luscher T Simpel D Linder L Haefely WE Substance P in human hand veins in vivo tolerance efficacy potency and mechanism of venodilator action Clin Pharmacol Ther 1996 60 435 443
27 O Donnell ME Owen NL Regulation of ion pumps and carriers in vascular smooth muscle Physiol Rev 1994 74 683 721
28 O Donnell ME Owen NE Sodium cotransport in vascular smooth muscle cells Blood Vessels 1991 28 138 146
29 O Donnell ME [3H]bumetanide binding in vascular endothelial cells Quantitation of Na K-Cl cotransporters J Biol Chem 1989 264 20326 20330
30 Flory JC Stewart GW The human erythrocyte Cl dependent Na K cotransport system as a possible model for studying the action of loop diuretics Br J Pharmacol 1982 75 183 188
31 Tundergan CF Fitzpatrick IM Rose JC Ramwell PW Kot PA Effect of cyclooxygenase inhibition on the pulmonary vasodilator response to furosemide J Pharmacol Exp Ther 1988 246 102 106
32 Collier JG Vallance P Endothelium-derived relaxing factor is an endogenous vasodilator in man Br J Pharmacol 1989 97 639-641

THE INFLUENCE OF THE MODE OF ADMINISTRATION OF HIGH DOSE FUROSEMIDE ON THE OCCURRENCE OF OTOTOXIC SIDE EFFECTS

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Submitted for publication

Abstract

Aim: To assess the influence of the mode of administration of high dose furosemide on the occurrence of furosemide induced ototoxicity (FIO)

Background: Ototoxity is reported to be a major side effect of furosemide and appears to be related to the serum furosemide concentration and probably to the unbound fraction High frequency audiometry (HFA) has been shown to be a very sensitive technique for the detection of ototoxicity

Methods: In 10 patients (2 female 8 male) with heart failure (n=2) chronic renal insufficiency (n=7) and nephrotic syndrome (n=1) high dose furosemide (mean (±SD) dosage 488 (±163 mg) was administered on three separate occasions orally as an intravenous bolus injection and as a continuous intravenous infusion respectively Serum furosemide as well as unbound furosemide concentrations were measured and audiometric evaluation included a questionnaire and HFA

Results: After oral ingestion no ototoxic side effects were reported or detected by HFA Short term (less than 15 minutes) side effects were reported after bolus injection (n=10) and after continuous infusion (n=3) One patient reported tinnitus after bolus injection while no one reported hearing loss HFA revealed a decrease in thresholds at t=5 min after bolus injection (n=8) and continuous infusion (n=3) while conventional speech and pure tone audiometry were unchanged At t=60 min after bolus injection FIO was still detectable in 6 patients while at t=240 min HFA was returned compared to base line levels in all patients Serum furosemide concentrations were significantly higher in patients with decrease of thresholds at high-frequency audiometry at t=5 min (FIO 81 ±49 μg ml no FIO 25 ±24 μg ml $p<0.01$) The mean unbound furosemide fraction was 2.2 ±1.0% and was independent of the total serum concentration or mode of administration

Conclusion: HFA appears to be more sensitive than both interview and conventional audiometric techniques for the detection of furosemide induced ototoxicity FIO occurs more frequently after intravenous bolus injection than during continuous intravenous infusion FIO was a short term completely reversible side effect in all patients in this study

INTRODUCTION

Loop diuretics are commonly applied in the management of pathological fluid retention in heart, liver and renal disease The efficacy of these drugs is beyond doubt Well-recognized side effects of loop diuretics are gastrointestinal symptoms (pancreatitis and mild nausea, vomiting and diarrhoea), dermatologic side effects (skin eruptions), metabolic disturbances (hypokalemia, hyponatremia, metabolic alkalosis, hyperuricemia, hyperglycemia), cardiovascular complications due to dehydration, and direct and indirect vascular effects, and - most frequently reported - ototoxic side effects [1]
Although the first large studies describing the intravenous administration of furosemide, a widely used loop diuretic, did not mention ototoxicity as a side effect, in the early 1970's reports of reversible furosemide-induced ototoxicity (FIO) appeared in literature [1-5] Not only reversible, but even sporadic cases of irreversible hearing loss due to the use of furosemide were observed [5-7] Especially patients with a decreased renal function, and thus a reduced clearance of the drug, who were treated with intravenous bolus injections of furosemide appeared to be at risk It was concluded that the maximum plasma furosemide concentration was an important determinant of the development of FIO importantly [8] Later, animal studies suggested that the unbound fraction of the drug was the major determinant of FIO [9,10] As a result clinicians became reluctant to use high dosages of furosemide, despite its excellent efficacy

In a previous study we showed that in patients with severe heart failure high dose furosemide administered as a continuous intravenous infusion was more efficacious than an equal dosage administered as an intravenous bolus injection [11] Moreover less ototoxic side effects seemed to occur when applying continuous intravenous infusion However, this study did not include a careful audiometric evaluation to assess the incidence and characteristics of FIO In the current study we used high-frequency audiometry (HFA), a sensitive tool for the early detection of ototoxicity, to evaluate the influence of the mode of furosemide administration on the occurrence of FIO We performed this study in a group of patients at risk for FIO patients suffering from heart failure or renal insufficiency, in need for high dose furosemide

Table 1 *Characteristics of the subjects*

Patient no	Sex m/f	Age (years)	Weight (kg)	Cause of illness	ECC (mL. min^{-1})	Renal replacement	Serum albumin (g. l^{-1})	Furosemide dosage (mg)
1	m	62	75	CRI	4	HD	42	250
2	m	39	81	CRI	3	HD	49	500
3	m	63	92	CHF	40		42	500
4	m	76	81	CRI	2	HD	41	500
5	m	66	75	CHF	26		41	750
6	m	72	74	CRI	15		45	750
7	f	23	61	NS	97		27	375
8	f	51	73	CRI	4	CAPD	37	500
9	m	60	76	CRI	22	-	42	250
10	m	41	107	CRI	29	-	40	500
Mean		55	80		24		40	488
SD		16	12		27		6	163
Range		23 76	61 107		2 97		27-49	250 750

Abbreviations are CAPD= continuous ambulant peritoneal dialysis, CHF= congestive heart failure, CRI= chronic renal insufficiency, f= female, HD= chronic intermittent hemodialysis, m= male, NS= nephrotic syndrome

We hypothesized that the use of high dose furosemide administered as a continuous intravenous administration causes less HO as compared with administration of the same dose as an intravenous bolus injection To get more insight into the relationship between the mode of administration and the development of HO, a pharmacokinetic evaluation was included in this study and total as well as unbound furosemide concentrations were measured

PATIENTS AND METHODS

Patients

This study was approved by the Medical Ethical Committee of St Joseph Hospital Veldhoven, and informed consent was obtained from all patients that were included The characteristics of these 10 patients are shown in Table 1 Mean (±SD) age was 55 ±16 years, mean body weight at the start of the study was 80 ±12 kg The mean endogenous creatinine clearance was 24 ±27 ml min Two patients suffered from chronic heart failure, one patient used high dose furosemide as a treatment for oedema caused by nephrotic syndrome, while seven patients were treated because of chronic renal insufficiency Of the latter group, four were dependent on renal replacement therapy Three of them underwent chronic intermittent hemodialysis, while one was treated with continuous ambulant peritoneal dialysis (CAPD) All patients were on high dose furosemide (i e daily dosage of at least 250 mg) for an average period of 433 ±577 days (range 20-1957 days) The mean daily dosage used in the study was 488 ±163 mg (range 250-750 mg) Before patients were included, they underwent an otological evaluation consisting of a questionnaire about prior ear diseases, ototoxic drug usage, and noise exposure, an otologic examination, and a baseline audiometric assessment including determination of pure tone thresholds from 250-8 000 Hz, pure-tone thresholds from 8 - 20 kHz (HFA) and a base-line speech audiogram

Study protocol

The study consisted of three parts, separated by time intervals of one week On each study day body weight was determined, blood samples were taken to determine serum sodium, potassium, chloride, albumin, creatinine, urea, uric acid and hemoglobin In addition 24-h urine was collected for determination of creatinine excretion All fluids containing furosemide (blood samples, syringes containing furosemide) were protected from light to avoid photochemical degradation On the first study day after an overnight fast each patient received his daily furosemide dosage as a single oral dosage Since an earlier study showed that in patients with heart failure peak plasma furosemide concentrations occurred 150 min after oral administration of the drug, blood samples were drawn at t=0 and t=150 min for determination of serum furosemide concentration (total and unbound concentration) Simultaneously HFA was performed

On the second study day an equal dosage was administered as an intravenous bolus injection The dosage was injected within two minutes Blood samples were drawn at t=0, 5, 10, 150 min and 240 min HFA of both ears was performed at t=5, 60, 240 and 480 min On the third study day furosemide was administered as a continuous intravenous infusion A loading dose, consisting of 20% of the total dosage was administered as an intravenous bolus injection within two minutes, followed by a continuous intravenous infusion of 8 hours, at a rate of 10% of the dose per hour The schedule for blood sampling and audiometric evaluation was identical to the one used on the second study day In addition HFA and blood sampling was also repeated on t=480 min In the patients on hemodialysis the dialysis schedule was kept constant during the entire study period and the time interval to the last hemodialysis treatment was equal on all the three study days for each patient The patient on CAPD changed the dialysate right before the administration of furosemide on each study day

Audiometric evaluation

Auditory function was monitored during the treatment by means of a questionnaire, pure-tone threshold audiometry and HFA. During each study day patients were repeatedly asked to answer a standard questionnaire on sensations (hearing loss, tinnitus, nausea, flushes, fear) occurring after ingestion or injection of furosemide. HFA (Demlar extended high frequency audiometer, Model 20K, ELB&associates, Hillsborough, USA, earphones HV/1A Plus) was performed according to the time schedule mentioned above at 8, 10, 12, 14, 16 and 18 kHz. Any disturbing noises were avoided within the room, when audiometry was carried out. All patients were alert and cooperative. Change of auditory function during therapy was determined as a difference between the initial and final assessment of the auditory thresholds. FIO determined by using the HFA was defined as an increase of ≥15 dB at one frequency or ≥10 dB at two frequencies in auditory threshold at least unilaterally. If the criteria for FIO were reached or if tinnitus or hearing loss was reported, pure-tone thresholds from 250 to 8 000 Hz were additionally determined.

Analytical methods

Serum furosemide concentrations were measured by high-performance liquid chromatography [13]. Unbound furosemide concentrations were determined after equilibrium dialysis during 5.5 hour at 37°C against isotonic phosphate buffered saline with pH 7.4. The dialysis cell contained 1 ml serum and 1 ml buffer, separated by a cellulose dialysis membrane (Cuprophan 150M) [14].

Data analysis

Plasma protein binding of furosemide was best modeled assuming one class of binding sites. The data were analyzed with the aid of the nonlinear regression program WinNonlin (Scientific Consulting, Inc., Apex NC, USA) according to the following equation, derived from the mass-action law:

$$C - C_u + n \cdot \frac{P}{K_d + C_u}$$

where C is the total serum furosemide concentration, C_u the unbound furosemide concentration in serum, n the number of protein binding sites, P the serum protein concentration, and K_d the dissociation constant of the drug-protein complex. Since furosemide binds nearly exclusively to albumin, for P the individual serum albumin concentrations of the patients were taken. The molecular weight of albumin was assumed to be 65,000.

Statistical analysis

Serum furosemide concentrations measured after intravenous bolus injection and continuous infusion, respectively were compared by using the two-tailed *t* test for paired data. Differences in serum furosemide concentrations between patients with and without FIO were analyzed by the two-tailed *t* test for unpaired data.

Ototoxic evaluation

None of the patients reported any ototoxic or related side effect after oral ingestion of furosemide. Immediately after administration of the intravenous bolus injection all (n=10) reported sensations that were directly related to the administration of furosemide, while only three patients experienced side effects (flushes in all three cases) after administration of the loading dose preceding the continuous intravenous infusion (see Table 2). Flushes were reported by all patients who experienced side effects. Tinnitus was reported by one patient after bolus injection, while other reported side effects after intravenous bolus injection were nausea (n=2), vomiting (n=1), fear (n=1), dyspnoea (n=2) and urge for defaecation (n=1). However, in all patients side effects were short-lasting and disappeared within 15 minutes. Remarkably, none of the patients experienced hearing loss at any moment during the three study days.

HFA evaluation revealed that after oral ingestion of furosemide none of the patients reached the criteria for FIO at t=150 min. Five minutes after intravenous bolus injection FIO was detected in 8 patients. The repeat of HFA at t=60 min showed that the threshold elevation in 6 patients persisted. At t=240 min HFA in all patients resulted in audiograms identical to baseline measurements. During administration of furosemide as a continuous intravenous infusion three patients reached the HFA criteria for FIO at t=5 min. Two of these patients experienced flushes at this moment. At t=60 min HFA thresholds returned to baseline levels in all three patients. At t=240 min, t=360 min and t=480 min no changes were observed. When FIO was observed, additionally pure-tone thresholds at 250-8 000 Hz were determined. However, comparison with baseline measurements did not reveal any changes within this frequency range in any of the patients.

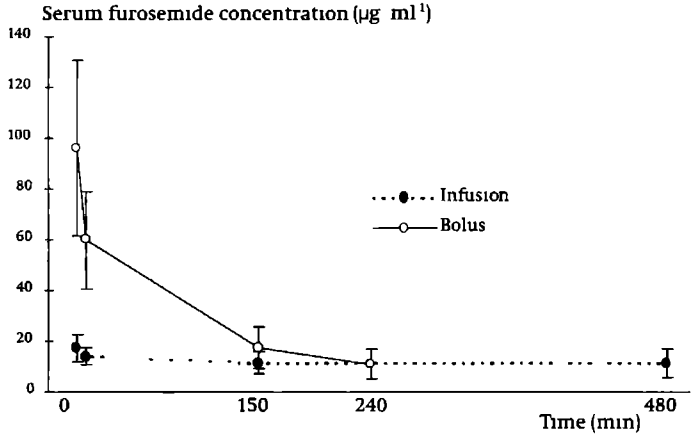

Figure 1 *Mean serum (±SD) furosemide concentrations after administration of furosemide as an intravenous bolus injection or as a continuous intravenous infusion (dosage 488 ±163 mg, range 250-750 mg)*

Pharmacokinetic evaluation

Mean serum electrolytes, hemoglobin, uric acid, urea, and creatinine did not differ significantly between the three study days. Neither did the mean serum albumin concentration (40 ±6 g. l^{-1}, range 27-49 g. l^{-1}). Figure 1 shows the mean serum furosemide concentrations after intravenous bolus injection and continuous intravenous infusion, respectively. At t=5 min and t=10 min mean serum furosemide concentrations were significantly higher after bolus injection than after continuous infusion. At t=150 min mean serum furosemide concentration was significantly higher after bolus injection compared with both oral and continuous infusion administration. Comparison of the mean furosemide concentration of the latter two at t=150 min showed no significant difference. The relationship between the serum furosemide concentration and the unbound furosemide concentration is shown in Figure 2. The estimated values for n and K_u were 1.14 ±0.11 and 3.8 ±0.6 μg. ml^{-1} (11.4 ±1.8 μM), respectively. The mean unbound fraction of furosemide did not differ significantly when the two modes of administration were compared (infusion: 2.2 ±1.1%, range 1.4 - 5.4%; bolus: 2.2 ±1.0%; range 1.5 - 5.4%). The variable time after injection did not influence the unbound fraction.

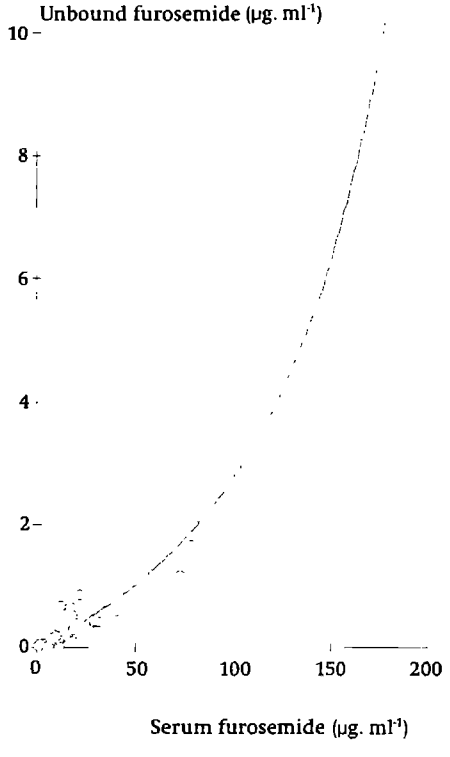

Figure 2. *Relationship between total and unbound serum furosemide concentrations. Concentrations were measured at t=5 min, t=15 min and t=150 min after intravenous bolus injection or continuous intravenous infusion*

Table 2 *Furosemide-induced ototoxicity as determined by subjective experiences of the patients and high frequency audiometry 150 minutes after oral administration and 5 minutes after intravenous administration as bolus injection and a continuous infusion*

	Sensations experienced after administration of furosemide			Increases of threshold at HFA		
Patient	Oral	Bolus	Continuous	Oral	Bolus	Continuous
no	t=150 min	t=5 min	t=5 min	t=150 min	t=5 min	t=5 min
1		Flush			+	+
2	-	Flush, Fear	-	-		
3		Flush Nausea	-		+	
4		Flush			+	
5		Flush, Dyspnoea Defaecation urge	-		+	
6		Flush, Dyspnoea	Flush	-	+	+
7	-	Flush, Tinnitus	Flush		+	
8		Flush, Nausea Vomiting	Flush		+	+
9	-	Flush	-		-	
10		Flush			+	-

Abbreviations HFA= high-frequency audiometry, t= time

Relationship between pharmacokinetics and high-frequency audiometry

The mean plasma furosemide concentration at t=5 min of the patients who reached the criteria for FIO, was significantly higher as compared with the group of patients without signs of FIO (81 ±49 μg ml^{-1} (FIO) versus 25 ±24 μg ml^{-1} (without FIO), $p < 0.01$) (see Figure 2) At t= 60 min the mean serum furosemide concentration appears to be significantly higher after bolus injection compared with continuous infusion At t=60 min HFA criteria were reached in 6 patients after intravenous bolus injection and in none of the patients after continuous intravenous infusion As shown in Figure 1 the mean serum furosemide concentration remained on a steady level throughout the infusion time during continuous infusion However, high frequency audiometry in the three patients that showed FIO after continuous intravenous infusion, returned to baseline levels at t=60 min and no signs of FIO occurred throughout the rest of the infusion time

Discussion

This study shows that FIO occurs less frequently when furosemide is administered as a continuous intravenous infusion as compared to administration of an equal dose as an intravenous bolus injection In this study we used HFA for the detection of FIO To our knowledge this is the first study analyzing FIO with HFA HFA has shown to be a sensitive tool that can be used for the detection of ototoxic damage induced by drugs like aminoglycosides, and platinum derivates [15,16] Both human and animal studies revealed that ototoxic damage is primarily present at the basal end of the cochlea, associated with a reduced hearing sensitivity in the higher-frequency region[17] This study establishes that HFA is more sensitive than history taking and the standard audiometric techniques, which confirms the results of other studies analyzing the ototoxic effects of other drugs [15,16]

Few studies have evaluated FIO by use of standard audiometric tools [3,18,19] *Heidland and Wigand* studied 35 patients with end stage renal failure [18] In 15 patients 1000 mg furosemide was administered intravenously within 40 min

Nine patients experienced transient hearing loss, which was confirmed by audiometry In 10 patients 600 mg of furosemide was infused within 40 min, causing minimal transient hearing loss in four of them In 10 patients the effect of chronic use (11-56 days) of orally administered high dose furosemide (daily dosage 500-1000 mg) was studied

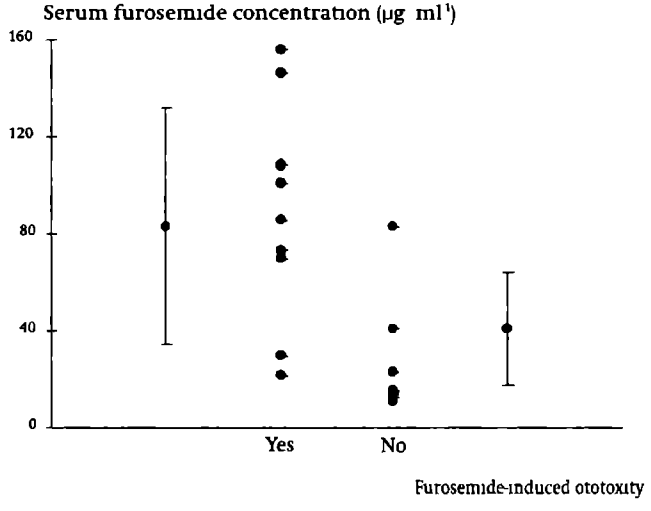

Figure 3 *Serum furosemide concentrations at t=5 min after administration of furosemide as an intravenous bolus injection or as a continuous intravenous infusion, preceded by a loading dose, in patients with and without furosemide-induced ototoxicity as determined with high frequency audiometry*

None of the patients developed hearing loss during this treatment and the audiometric findings did not change importantly during this treatment *Van Olden et al* reported on the acute and long-term effects of the use of high dose furosemide (daily oral dosage 250-2000 mg) in chronic hemodialysis patients [19] The serum furosemide concentrations ranged from 11 2 to 35 8 μg ml⁻¹ Three monthly audiometry during chronic treatment did not show any ototoxicity In a large meta-analysis comparing the adverse reactions to bumetanide and furosemide in patients with heart failure, renal or hepatic disease, the overall incidence of drug-related audiometric determined hearing loss was 1 1% in the bumetanide group and 6 4% in the furosemide group [20]

In this study the clinically recognized FIO appeared to be a short-term and completely reversible effect lasting no longer than 15 minutes However, only one patient reported tinnitus and none of the patients reported hearing loss, while all patients reported "non-ototoxic" side effects like eg flushes, fear or dyspnoea after intravenous bolus injection Three patients reported flushes during continuous intravenous infusion of furosemide On the other hand, HFA revealed an increase in thresholds in the high frequency range in 8 patients after intravenous bolus injection and in 3 patients after continuous intravenous infusion, respectively Moreover, alterations in HFA lasted shorter than one hour in 5 patients, but persisted for at least 60 minutes in 6 patients, the latter in all cases after intravenous bolus injection Pure-tone audiometry and speech audiograms performed when HFA indicated FIO revealed no changes at all

In animal studies, using endocochlear potentials to establish ototoxicity, FIO occurred 5 to 15 minutes after the intravenous dose and corresponded with the time of maximum perilymph furosemide concentrations [21,22] It was also shown that endocochlear potentials remained depressed as long as perilymph furosemide concentrations exceeded a threshold value of 1 3 µg ml In chinchillas the elimination of furosemide from the perilymph appeared to be mono-exponential [22] Furosemide perilymph concentration parallelled the serum concentration within a wide range [22] With a perilymph serum gradient of 1 65 and a threshold perilymph furosemide concentration of 1 3 µg ml^{-1} this means that FIO did not occur as long as the serum furosemide concentration remained below approximately 80 µg ml^{-1}

In the group of patients that developed FIO the plasma furosemide concentration was significantly higher than in the group that developed no FIO (Figure 2) Since administration of furosemide as an intravenous loading dose followed by a continuous infusion results in lower serum furosemide concentrations, it seems obvious that this mode of administration less frequently causes FIO On the other hand, FIO was detected in some patients after continuous infusion, despite the relatively low serum furosemide concentrations In other words, we were not able to define a threshold plasma furosemide concentration Interindividual differences and the relatively small number of patients studied may be responsible for this

When FIO appeared during continuous intravenous infusion of furosemide, it was only present for a short time, although the serum furosemide concentration remained stable throughout the infusion period This suggests that the serum furosemide concentration is not the only determinant in the development of FIO, but also the rate of change in serum (and probably endolymph) furosemide concentration This hypothesis is supported by the observation that after oral administration plasma furosemide concentrations were in the same range as the concentrations after continuous intravenous infusion while no clinical recognizable FIO occurred following the former mode of administration Another explanation could be that, when the serum furosemide concentration rises above a certain threshold value an ototoxic effect is induced that is transient irrespective of the serum furosemide concentration Since in animal studies continuous intravenous infusion never has been applied, this hypothesis is yet to be confirmed However, in chinchillas the recovery time was shown to be positively correlated with the administered furosemide dosage [22] In one study in cats repeated intravenous doses of furosemide administered with an interval of one hour resulted in increasing depression of cochlear action potentials However, complete recovery in all cases occurred within one hour, even after repeated doses [23]

All patients had been using high dose furosemide for a longer period of time preceding the study This means that irreversible hearing loss already might have occurred before the start of the study On the other hand, the audiometric evaluation performed before the start of this study was within normal age-corrected limits in all patients[17] Moreover, review of the literature shows that most of the cases of FIO reported concern reversible instead of irreversible FIO [5-7] This means that, regarding the frequent use of furosemide in clinical practice, irreversible ototoxicity solely attributable to furosemide is an extremely rare side effect Finally, in animals receiving furosemide chronically, no change was observed in baseline endocochlear potential, fall in endocochlear potential or time to complete recovery of endocochlear potential after intravenous furosemide injection, respectively, as compared to animals that were not pretreated [22]
The exact mechanism of FIO is not known The most consistent finding in histopathologic studies is formed by reversible structural changes in the stria vascularis [24-27] The time course of these changes parallelled the alterations in endocochlear potentials

It was shown that changes in endocochlear potential corresponded better with the furosemide perilymph concentration than the alterations of inner ear fluid electrolyte concentrations induced by furosemide [21,22] Moreover, changes in endocochlear potentials could be attenuated by coadministration of organic acids like salicylates, probenicid and penicillin, suggesting that FIO is mediated by an organic acid uptake mechanism in the cochlea [28] Probenecid reduced penetration of furosemide into perilymph [29] Two studies show that the FIO is determined by the quantity of unbound furosemide and by reducing this the absolute amount of unbound serum furosemide FIO was alleviated [9,10] We determined both unbound and total serum furosemide concentration However, our results do not allow to draw a conclusion as to whether FIO is mainly determined by the unbound furosemide concentration, because total furosemide concentration and unbound furosemide concentration were strongly correlated (Figure 3) However, our in vivo observations suggest that the binding of furosemide to serum albumin is saturable, which means that the risk at FIO increases exponentially when patients receive very high dosages of furosemide when administered as an intravenous bolus injection It should be noted that in the patients studied, the mean unbound furosemide fraction was approximately 2 2% while in healthy volunteers on conventional dosages this is reported to be in the range of 1-4% [30] In patients with heart failure and renal failure using conventional dosages of furosemide the unbound fraction of furosemide was reported to be higher [31,32]

In conclusion HFA appears to be a sensitive tool for the detection of FIO FIO occurs less frequently, when furosemide is given as a continuous intravenous infusion compared with intravenous bolus injection For this reason and because of its greater diuretic efficacy the continuous intravenous infusion of furosemide is the mode of administration that is to be preferred in the clinical treatment of congestive heart failure, especially when high dosages of furosemide are needed FIO appeared to be a short-term completely reversible phenomenon in all patients in this study

References

1 Cooperman J and Band Rubin JL Toxicity of ethacrynic acid and furosemide Am Heart J 1973 85 831 834
2 Schwartz GH David DS Riggio RR Stenzel KH and Rubin AL Ototoxicity induced by furosemide N Engl J Med 1970 282 1413 1414
3 Heidland A and Wigand ME [Hearing loss induced by the use of high doses of furosemide in the treatment of uremia] Klin Wochenschr 1970 48 1052 1056
4 Venkateswaran PS Transient deafness from high doses of frusemide Br Med J 1971 4 113-114
5 Lloyd Mostyn RH and Lord IJ Ototoxicity of intravenous frusemide Lancet 1971 2 1156
6 Quick CA and Hoppe W Permanent deafness associated with furosemide administration Ann Otol Rhinol Laryngol 1975 84 94-101
7 Gallagher KJ and Jones JK Furosemide-induced ototoxicity Ann Intern Med 1979 91 744-745
8 Rybak LP Ototoxicity of loop diuretics Otolaryngol Clin North Am 1993 26 829-844
9 Ikeda K and Morizono T Effect of albumin bound furosemide on the endocochlear potential of the chinchilla Alleviation of furosemide induced ototoxicity Arch Otolaryngol Head Neck Surg 1989 115 500-502
10 Rybak LP Whitworth C and Scott V Furosemide ototoxicity is enhanced in analbuminemic rats Arch Otolaryngol Head Neck Surg 1993 119 758 761
11 Dormans TP van Meyel JJ Gerlag PG Tan Y Russel FG and Smits P Diuretic efficacy of high dose furosemide in severe heart failure bolus injection versus continuous infusion J Am Coll Cardiol 1996 28 376 382
12 van Meyel JJ Gerlag PG Smits P Russel FG Tan Y Van Ginneken CA et al Absorption of high dose furosemide (frusemide) in congestive heart failure Clin Pharmacokinet 1992 22 308 318
13 Russel FGM Tan Y Meyel van JJM Gribnau FWJ and Ginneken van CAM Solid phase extraction of furosemide from plasma and urine and subsequent analysis by high-performance liquid chromatography J Chromat 1989 496 234-241
14 van den Ouweland FA Gribnau FWJ Tan Y Van Ginneken CA and van de Putte LBA Hypoalbuminaemia and naproxen pharmacokinetics in a patient with rheumatoid arthritis Clin Pharmacokinet 1986 11 511 515
15 Blaser J Simmen HP Thurnheer U Konig C and Luthy R Nephrotoxicity high frequency ototoxicity efficacy and serum kinetics of once versus thrice daily dosing of netilmicin in patients with serious infections J Antimicrob Chemother 1995 36 803 814
16 Dreschler WA van der Hulst RJ Tange RA and Urbanus NA Role of high-frequency audiometry in the early detection of ototoxicity II Clinical Aspects Audiology 1989 28 211 220
17 Dreschler WA van der Hulst RJ Tange RA and Urbanus NA The role of high frequency audiometry in early detection of ototoxicity Audiology 1985 24 387 395
18 Wigand ME and Heidland A Ototoxic side effects of high doses of frusemide in patients with uraemia Postgrad Med J 1971 47 Suppl 54-Suppl 56
19 van Olden RW van Meyel JJ and Gerlag PG Acute and long term effects of therapy with high dose furosemide in chronic hemodialysis patients Am J Nephrol 1992 12 351 356
20 Tuzel IH Comparison of adverse reactions to bumetanide and furosemide J Clin Pharmacol 1981 21 615-619
21 Brusilow SW Propranolol antagonism to the effect of furosemide on the composition of endolymph in guinea pigs Can J Physiol Pharmacol 1976 54 42 48
22 Green JP Rybak LP Mirkin BL Juhn SK and Morizono T Pharmacologic determinants of ototoxicity of furosemide in the chinchilla J Pharmacol Exp Ther 1981 216 537 542
23 Mathog RH Thomas WG and Hudson WR Ototoxicity of new and potent diuretics A preliminary study Arch Otolaryngol 1970 92 7 13
24 Forge A and Brown AM Ultrastructural and electrophysiological studies of acute ototoxic effects of furosemide Br J Audiol 1982 16 109 116
25 Quick CA and Duvall AJ Early changes in the cochlear duct from ethacrynic acid an electronmicroscopic evaluation Laryngoscope 1970 80 954-965
26 Pike DA and Bosher SK The time course of the strial changes produced by intravenous furosemide Hear Res 1980 3 79 89
27 Arnold W Nadol JBJ and Weidauer H Ultrastructural histopathology in a case of human ototoxicity due to loop diuretics Acta Otolaryngol Stockh 1981 91 399 414
28 Rybak LP and Whitworth C Some organic acids attenuate the effects of furosemide on the endocochlear potential Hear Res 1987 26 89-93
29 Rybak LP Green TP Juhn SK and Morizono T Probenecid reduces cochlear effects and perilymph penetration of furosemide in chinchilla J Pharmacol Exp Ther 1984 230 706-709
30 Ponto LL and Schoenwald RD Furosemide (frusemide) A pharmacokinetic pharmacodynamic review (Part II) Clin Pharmacokinet 1990 18 381-408
31 Andreasen F and Mikkelsen F Distribution elimination and effect of furosemide in normal subjects and in patients with heart failure Eur J Clin Pharmacol 1977 12 15 22
32 Andreasen F Hansen HF and Mikkelsen F Pharmacokinetics of furosemide in anephric patients and in normal subjects Eur J Clin Pharmacol 1978 13 41 48

CHAPTER ELEVEN

SUMMARY

Summary

This thesis deals with various aspects of high dose furosemide Furosemide is a loop diuretic applied in several disease states, characterized by oedema Standard dosing schedules of furosemide range between 40 and 240 mg per day We defined high dose furosemide as a daily dosage of 250-4000 mg Although it has been established more than twenty years ago that high dose furosemide is effective in some patients that do not respond to conventional dosages of furosemide several important questions still remain unanswered The studies described in this thesis were performed to obtain more insight in both the effects and side effects of the use of high dose furosemide Three major aspects are studied

- The diuretic efficacy of high dose furosemide and the management of diuretic resistance to high dose furosemide in chronic heart failure
- The vascular effects of furosemide
- The ototoxic side effects of high dose furosemide and its relationship to the mode of administration

Chapter 2

In earlier studies it has been shown that high dose furosemide (i e a daily dosage larger than 240 mg) effectively corrects the hydration status in patients with congestive heart failure unresponsive to conventional dosages furosemide We conducted a study to obtain insight in the efficacy and safety of continuous intravenous administration of high dose furosemide in the treatment of patients with severe congestive heart failure unresponsive to conventional dosages of furosemide The theoretical advantage of this manner of administration is an increased efficacy, combined with less ototoxic side effects In this open uncontrolled study continuous intravenous infusion appeared to be a safe, controllable and efficacious tool in the treatment of chronic congestive heart failure

Chapter 3

Here we compared the efficacy of high dose furosemide administered as a continuous intravenous infusion with the administration as an equivalent intravenous bolus injection in patients with severe heart failure Continuous intravenous administration of high dose furosemide appeared to be more efficacious than intravenous bolus injection Ototoxic side effects were recorded more frequently after intravenous bolus injection However, this study did not include a valid audiometric evaluation

Chapter 4

It appears that a small group of patients suffering from severe heart failure with progression of the disease, finally become unresponsive to high dose furosemide These patients often are severely symptomatic We asked ourselves whether this group of patients might benefit from dehydration by means of chronic intermittent hemofiltration and/or hemodialysis The results of this treatment were disappointing in terms of both survival time and quality of life On the basis of these results we concluded that in patients with severe congestive heart failure with diuretic resistance to high dose furosemide, chronic intermittent hemofiltration and hemodialysis is only of limited value and should only be used in case of a remediable cause of heart failure or as a bridge to heart transplantation

Chapter 5

We treated patients with severe heart failure unresponsive to a pharmacological regimen including high dose furosemide by adding hydrochlorothiazide to high dose furosemide Since the early 1970's it is known from several clinical studies that loop diuretics and thiazide drugs acting on the distal convoluted tubule act synergistically However, it is unknown whether this synergism is still present in patients unresponsive to high dose furosemide In this study addition of hydrochlorothiazide to high dose furosemide appeared to be a very powerful diuretic combination, causing a reduction of the extracellular fluid compartment in all treated patients Hypokalemia and dehydration were the most serious side effects of this therapy

Chapter 6

Animal studies have suggested that chronic treatment with loop diuretics induces an increased sodium reabsorbing capacity of the distal convoluted tubule, limiting the natriuretic effect of the administration of a loop diuretic drug
Moreover, it was shown that thiazides could block this increase in sodium reabsorbing capacity of the distal convoluted tubule This means that the natriuretic response to loop diuretics may be preserved, when a thiazide is added to the loop diuretic drug To study whether these mechanisms are present in humans and whether this may be of clinical relevance we performed an experiment in healthy volunteers Although we could prove that the natriuretic effect of furosemide was blunted after chronic use of this drug, we did not find a preservative effect of coadministration of hydrochlorothiazide on the natriuretic effect of furosemide in the studied population

Chapter 7

An overview of the approach to diuretic resistance in severe heart failure is described Emphasis is put on the value of the use of combination diuretic therapy

Chapter8

We review the literature on the vascular effects of loop diurectics On basis of the literature available it can be concluded that several factors may be involved in the arterial vascular response to loop diuretics, including the degree of salt depletion, renin, angiotensin II and prostaglandins while the venous vascular response appeared to be a genuine direct effect However, literature is not conclusive as to whether furosemide exerts direct vasoactivity in vivo

Chapter 9

To further elucidate the direct vascular effects of furosemide we performed a number of experiments in healthy human volunteers The effects on the arterial vascular wall were examined using the perfused forearm technique, while the venous effects of furosemide were evaluated by means of a linear variable differential transducer measuring the distensibility of a dorsal hand vein A direct effect of furosemide on the arteries in the forearm could not be detected, while a dose-dependent direct venodilator effect on the dorsal hand vein existed, which appeared to be mediated by local vascular prostaglandins

CHAPTER 10

In the last part a study on the ototoxic effects of furosemide is described. Soon after the introduction of furosemide, reports on otoxic side effects of this drug appeared in literature. While only a very small number of cases of irreversible ototoxicity directly related to the use of furosemide were described, many clinicians fear this complication of the treatment with diuretics. Most of the studies on furosemide-induced ototoxicity are performed in animals, and few human data are available. In chapter 10 the results of an audiometric evaluation of the effect of different modes of administration of high dose furosemide in patients with severe heart failure, end stage renal failure, or nephrotic syndrome are presented. It is shown that furosemide-induced ototoxicity, though often without otologic symptoms (deafness, tinnitus, vertigo) and always completely reversible, often occurs after administration of high dose furosemide. By administration of furosemide as a continuous intravenous infusion instead of an intravenous bolus injection, the incidence of furosemide-induced ototoxicity can be substantially reduced. There appeared to be a clear relationship between the peak serum furosemide concentration and the presence of ototoxicity, as determined by high-frequency audiometry.

SAMENVATTING

Samenvatting

In dit proefschrift staat een aantal aspecten van de effecten van hoge doseringen furosemide centraal Furosemide is een lisdiureticum dat toegepast wordt bij de behandeling van een aantal ziektebeelden, die als gemeenschappelijk kenmerk de retentie van vocht oftewel de ontwikkeling van oedeem- heeft Gebruikelijke orale doseringen furosemide kunnen variëren van 40 mg tot 240 mg per dag Met de term "hoge doseringen" furosemide wordt in dit proefschrift bedoeld dagdoseringen, variërend van 250 mg tot 4000 mg Het is ruim twintig jaar bekend dat het gebruik van hoge doseringen furosemide effectief kan zijn, wanneer er na toediening van gebruikelijke doseringen furosemide een onvoldoende diuretische respons wordt gezien De kennis omtrent de toepassing van hoge doseringen furosemide is echter nog steeds onvolledig. De studies, beschreven in dit proefschrift, werden uitgevoerd om meer inzicht te verwerven in de effecten en bijwerkingen van de toepassing van hoge doseringen furosemide in de klinische praktijk
Drie onderdelen werden bestudeerd en beschreven

- De diuretische effectiviteit van hoge doseringen furosemide en de behandeling van diureticaresistentie bij patienten met chronisch hartfalen
- De vasculaire effecten van furosemide
- De ototoxische bijwerking van het gebruik van hoge doseringen furosemide en de invloed hierop van de wijze van toediening

Hoofdstuk 2

Eerdere studies hebben aangetoond dat de toediening van hoge doseringen furosemide resulteerde in een correctie van de hydratietoestand van patienten met chronisch hartfalen, die na het gebruik van conventionele doseringen furosemide onvoldoende diuretische respons vertoonden Deze studie werd uitgevoerd om meer inzicht te krijgen in de effectiviteit en de veiligheid van de toediening van hoge doseringen furosemide als continu toegediende intraveneuze infusie bij de behandeling van bovengenoemde patientengroep De theoretische voordelen van deze toedieningswijze, in vergelijking met toediening als intraveneuze bolusinjecties, zijn een toename in effectiviteit en een kleinere kans op ototoxische bijwerkingen In deze ongecontroleerde studie bleek continue intraveneuze infusie van hoge doseringen furosemide een veilige, stuurbare en effectieve behandelingsoptie voor patienten met chronisch congestief hartfalen

Hoofdstuk 3

De effectiviteit van twee manieren van toediening van equivalente hoge doseringen furosemide werd vergeleken bij patienten met ernstig chronisch hartfalen continue intraveneuze infusie versus intraveneuze bolusinjectie Toegediend als continue intraveneuze infusie bleken hoge doseringen furosemide effectiever te zijn Ototoxische bijwerkingen werden door de patienten vaker gemeld na intraveneuze bolusinjectie Daarbij dient aangetekend te worden dat in deze studie ototoxiciteit niet geevalueerd werd met behulp van een valide audiometrisch onderzoek

Hoofdstuk 4

In de klinische praktijk blijkt dat sommige patienten met ernstig chronisch hartfalen, uiteindelijk niet meer of onvoldoende reageren op de behandeling met hoge doseringen furosemide Dit gaat vaak gepaard met ernstige symptomatologie

De vraag was of deze groep patienten baat heeft bij de correctie van de hydratietoestand met behulp van chronisch intermitterende hemofiltratie en/of hemodialyse De resultaten van deze behandelingsvorm waren teleurstellend, zowel wat betreft de invloed op de kwaliteit van leven als op de overleving Op grond van deze resultaten luidde de conclusie dan ook dat de waarde van chronisch intermitterende hemofiltratie en/of hemodialyse beperkt is bij de behandeling van patienten met chronisch gedecompenseerd hartfalen, met onvoldoende respons op de behandeling met hoge doseringen furosemide Naar onze mening dient deze behandelingsoptie voor deze patientengroep dan ook alleen toegepast te worden, wanneer er sprake is van een reversibele vorm van hartfalen of in een overbruggingsfase naar een harttransplantatie

HOOFDSTUK 5

Op zoek naar een effectieve behandeling voor patienten met ernstig chronisch hartfalen, bij wie toepassing van hoge doses furosemide onvoldoende effect sorteert, behandelden we deze groep patienten door het thiazidediureticum hydrochloorthiazide toe te voegen aan de hoge doses furosemide In de afgelopen drie decennia hebben diverse studies aangetoond dat lisdiuretica en thiazidediuretica (werkzaam in de distale tubulus) synergistisch zijn Het was echter onduidelijk of deze synergie nog steeds aanwezig is wanneer de diuretische respons op hoge doseringen furosemide insufficient is In deze studie bleek de combinatie van hoge doseringen furosemide en hydrochloorthiazide ook in deze patientengroep een zeer krachtige diuretische behandelmethode, resulterend in een afname van oedeem bij alle behandelde patienten Hypokaliemie en dehydratie vormden de belangrijkste bijwerkingen

HOOFDSTUK 6

In dierexperimenteel onderzoek is aangetoond dat chronische behandeling met lisdiuretica leidt tot een toename van de natriumreabsorberende capaciteit van de distale tubulus Deze functionele adaptatie van dit segment van het nefron leidt tot een reductie van het natriuretische effect van furosemide Bovendien bleek dat de gelijktijdige toediening van een thiazidediureticum de toename in natriumreabsorberende capaciteit kon voorkomen Dit betekent dat de natriuretische respons op toediening van een lisdiureticum behouden zou kunnen worden door gelijktijdige toediening van een thiazidediureticum Het is onduidelijk of dit mechanisme ook aanwezig is bij de mens, en zo ja, of dit mechanisme klinisch relevant is Om hier meer inzicht in te krijgen voerden we de in dit hoofdstuk beschreven studie bij gezonde jonge vrijwilligers uit Hoewel we in deze studiepopulatie konden aantonen dat het natriuretisch effect van furosemide 'uitdooft' bij chronisch gebruik van dit diureticum, bleek uit deze studie niet dat door gelijktijdige toediening van hydrochloorthiazide, het natriuretische effect van furosemide "gefixeerd" kon worden

HOOFDSTUK 7

In dit hoofdstuk wordt een overzicht gegeven van de behandeling van diureticaresistentie bij patienten met ernstig hartfalen, waarbij de nadruk ligt op de toepassing van combinaties van diuretica

HOOFDSTUK 8

In dit hoofdstuk wordt een literatuuroverzicht gegeven van de studies naar de vasculaire effecten van lisdiuretica Op basis hiervan kan vastgesteld worden dat waarschijnlijk diverse factoren een rol spelen bij de arteriele vasculaire respons op lisdiuretica, onder andere de mate van zoutdepletie, de plasma renine activiteit, angiotensine II en prostaglandines De veneuze vasculaire respons lijkt door een direct effect van het diureticum op de veneuze vaatwand bepaald te worden Wat betreft de aanwezigheid van direct vasculaire effecten van furosemide in vivo, is de literatuur is echter niet een duidig

HOOFDSTUK 9

Bij gezonde vrijwilligers werden een aantal studies uitgevoerd, met als doel meer inzicht te verkrijgen in de direct vasculaire effecten van furosemide De effecten van furosemide op de arteriele vaatwand werden bestudeerd met behulp van het onderarmsmodel, de effecten op de veneuze vaatwand werden bestudeerd met behulp van de 'lineair variable differential transducer', met deze techniek kunnen variaties in de diameter van een vene op de handrug bepaald worden Een direct effect van furosemide op de arteriele vaatwand kon niet vastgesteld worden Wel bleek er een dosisafhankelijk direct venodilaterend effect te bestaan, hetgeen leek te berusten op de lokale afgifte van prostaglandines

HOOFDSTUK 10

In dit hoofdstuk wordt een studie beschreven, waarin de ototoxische effecten van furosemide geevalueerd werden Ototoxische bijwerkingen werden al kort na de introductie van furosemide in de klinische praktijk beschreven Hoewel het merendeel van de beschreven casus reversibele ototoxiciteit vermeldde, is er echter ook een zeer beperkt aantal gevallen bekend, waarbij irreversibele ototoxiciteit het directe gevolg was van het gebruik van furosemide Het gevolg hiervan is dat veel klinici vanwege deze potentiele bijwerking huiverig zijn om furosemide, en met name hoge doseringen furosemide voor te schrijven Het merendeel van het onderzoek naar door furosemide geinduceerde ototoxiciteit is verricht bij proefdieren In hoofdstuk 10 worden de resultaten weergegeven van een audiometrische evaluatie van de invloed van de wijze van toediening van hoge doseringen furosemide op de ototoxische bijwerking bij patienten met chronisch hartfalen, chronische nierinsufficientie of nefrotisch syndroom Met behulp van hoge tonen audiometrie kon worden aangetoond dat het gebruik van hoge doseringen furosemide vaak gepaard gaat met ototoxiciteit, weliswaar meestal zonder otologische symptomatologie (doofheid, tinnitus, vertigo) De waargenomen ototoxische schade bleek altijd volledig reversibel Door furosemide toe te dienen als continue intraveneuze infusie in plaats van intraveneuze bolusinjecties, kan de incidentie van door furosemide geinduceerde ototoxiciteit in belangrijke mate worden beperkt Er bleek een duidelijk verband te bestaan tussen de maximale serum furosemide concentratie en het optreden van ototoxiciteit

Dankwoord

Het onderzoek, beschreven in dit proefschrift, voltrok zich voor een belangrijk deel in de 'verloren' uurtjes, in de avonduren, tijdens rustige diensten, uitgevallen poli-bezoeken, 'compensatiedagen', etc In de afgelopen 6 jaren kwam het onderzoek vaak op het tweede plan, naast opleidings-, gezins- en sociale verplichtingen, maar bleef steeds prominent aanwezig Het geeft dan ook veel voldoening, dat het is afgerond Om op deze manier onderzoek te kunnen doen, moet aan een aantal voorwaarden worden voldaan

De belangrijkste voorwaarde is een stimulerende en inspirerende omgeving Met name in de persoon van dr P G G Geilag werd hierin ruimschoots voorzien Beste Paul, voordat er een letter op papier stond had je het al over het schrijven van 'een boekje' Toen lachte ik je uit, nu ben ik blij dat ik je uiteindelijk gelijk moet geven Je zorgvuldige en accurate manier van werken, maar vooral je betrokkenheid zijn, zowel in de klinische als in de wetenschappelijke praktijk, dagelijks een voorbeeld voor mij

Daarnaast is medewerking en begrip van de omgeving van groot belang Paul Smits en Frans Russel wil ik bedanken voor de mogelijkheid het in Veldhoven gestarte onderzoek voort te zetten en uit te bouwen tot dit proefschrift
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Niek en Thijs jullie visie op dit alles kan waarschijnlijk als volgt samengevat worden (vrij naar Annie M G Schmidt) "proefschriften zijn aardig, maar wat moeten we d'r mee?" Felice, misschien was je het wel deels met Niek en Thijs eens, maar je hebt dat nooit laten merken Om aan te sluiten bij het bovengenoemde citaat " nu kunnen we verder gaan op onze kleine voetjes, naar de wildernis, want daar zijn de kaketoetjes"

CURRICULUM VITAE

De schrijver van dit proefschrift werd op 6 april 1961 in Spaubeek (L) geboren In 1979 behaalde hij het gymnasium-β diploma aan het St. Michiellyceum te Geleen. Het lot verhinderde hem in de daaropvolgende twee jaar te beginnen met de studie geneeskunde. In deze periode studeerde hij achtereenvolgens aan de Akademie voor Fysiotherapie te Heerlen en aan de Landbouw Hogeschool te Wageningen (N-propaedeuse). Vanaf 1981 studeerde hij geneeskunde aan de Katholieke Universiteit te Nijmegen. Het doctoraalexamen behaalde hij in 1986, het artsexamen in 1989. In het kader van de vervangende dienstplicht verrichtte hij van 1989 tot 1990 onderzoek op het gebied van het cholesterolmetabolisme in het Laboratorium voor Interne Geneeskunde van het Academisch Ziekenhuis Nijmegen (hoofd: Dr. P.N.M. Demacker). Van 1990 tot 1994 was hij werkzaam als arts-assistent werkzaam binnen de afdeling interne geneeskunde van het St. Joseph Ziekenhuis te Veldhoven. Vanaf maart 1991 tot mei 1994 werd aldaar de opleiding tot internist gevolgd (opleider: Dr. P.G.G. Gerlag). In deze periode werd de basis gelegd voor dit proefschrift. Het resterende deel van de opleiding tot internist werd gevolgd in het Academisch Ziekenhuis Nijmegen (opleider: Prof. Dr. J.W.M. van der Meer). Registratie als internist vond plaats op 1 maart 1997. Van 1 juli 1996 tot 1 mei 1998 was hij in het kader van het aandachtsgebied intensive care geneeskunde werkzaam op de afdeling intensive care van het Academisch Ziekenhuis Nijmegen (opleider: Dr. F.W. Santman). Registratie voor het aandachtsgebied intensive care geneeskunde vond plaats op 1 januari 1998. Vanaf 1 mei 1998 is hij als internist-intensivist werkzaam in het Atrium medisch centrum te Heerlen. Hij is getrouwd met Felicia Harteveld.
Zij hebben twee zonen, Niek (1992) en Thijs (1994).

STELLINGEN

behorende bij het proefschrift

Diuretic, vascular and ototoxic effects of high dose furosemide

van

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STELLINGEN

Bij de behandeling van patienten met ernstig chronisch hartfalen heeft een hoge dosis furosemide, toegediend als continue intraveneuze infusie, een groter natriuretisch effect dan een gelijke hoeveelheid furosemide, toegediend als een eenmalige intraveneuze bolusinjectie.
Dit proefschrift

Chronisch intermitterende hemofiltratie of hemodialyse is van beperkte waarde bij de behandeling van patienten met ernstig gedecompenseerd chronisch hartfalen, die onvoldoende reageren op het gebruik van hoge doseringen furosemide.
Dit proefschrift

Toevoeging van een thiazidepreparaat aan een hoge dagdosis furosemide is een effectieve vorm van diuretische behandeling van patienten met ernstig gedecompenseerd chronisch hartfalen, die onvoldoende reageren op het gebruik van hoge doseringen furosemide alleen.
Dit proefschrift

Furosemide heeft een dosisafhankelijke venodilaterende werking, die berust op lokale prostaglandineproductie
Dit proefschrift

Door furosemide geinduceerde, reversibele ototoxische effecten treden minder vaak op bij toediening van hoge doseringen furosemide in de vorm van een continue intraveneuze infusie dan bij toediening als intraveneuze bolusinjectie
Dit proefschrift

Geprotocolleerde poliklinische behandeling en begeleiding van patienten met ernstig chronisch hartfalen door een gespecialiseerd team leidt niet alleen tot een verbetering van de functionele status en een reductie in ziekenhuisopnames, maar kan ook kosteneffectief zijn.
J Am Coll Cardiol 1997;30.725-732
Circulation 1997;96.2842-2848

De bepaling van de intra-abdominale druk bij patienten, na een ernstig abdominaal trauma of na een grote intra-abdominale ingreep, verschaft op eenvoudige wijze te verkrijgen objectiveerbare informatie, van belang voor het tijdig vaststellen van de indicatie voor een (re)laparotomie.
Am J Surg 1997; 174:667-673

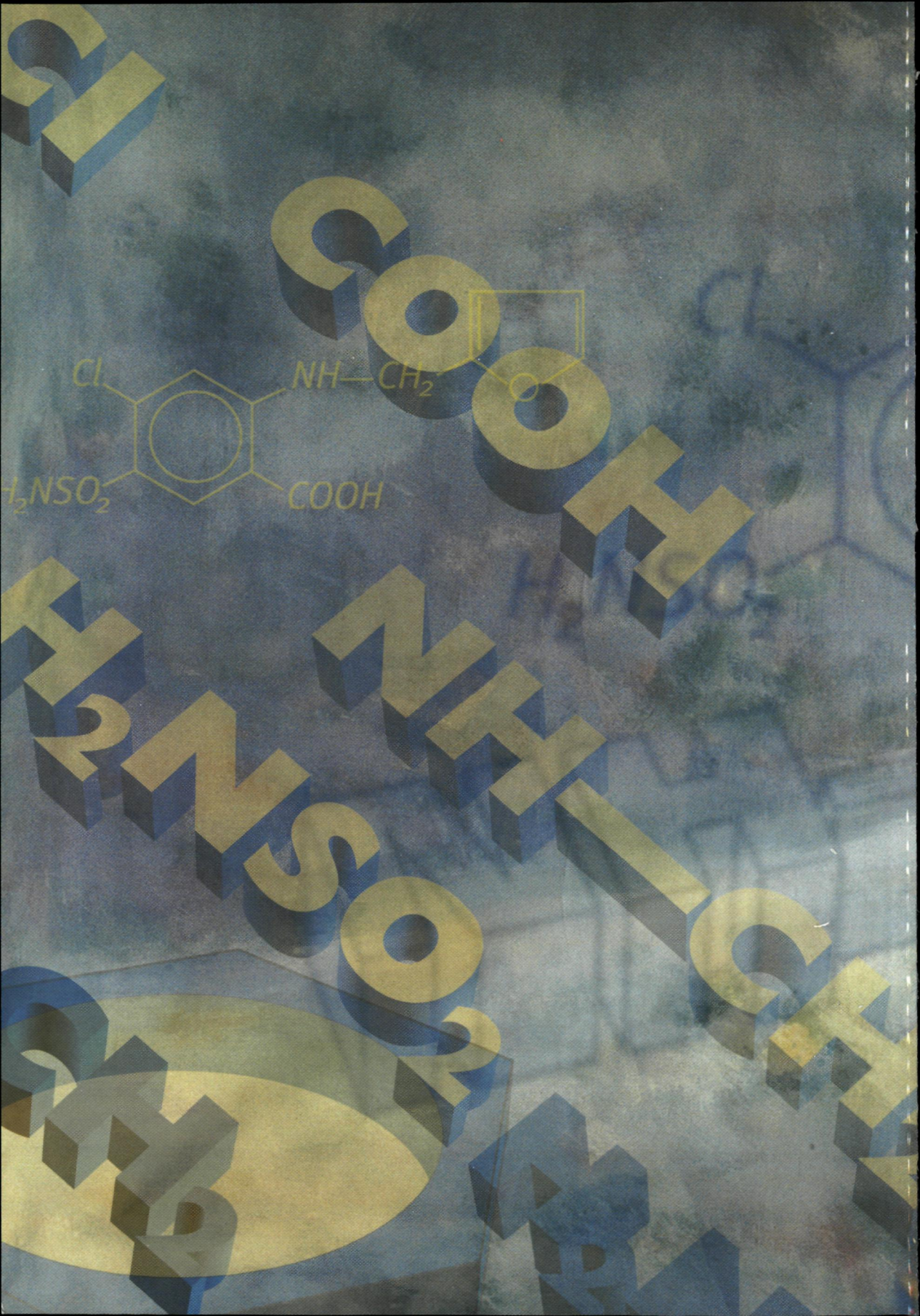
De Limburgse stinkkaas is niet alleen een lokale delicatesse, maar mogelijk ook een effectief middel ter profylaxe van malaria-infectie.
Lancet 1996; 348: 1322

Een belangrijk nadelig gevolg van de afschaffing van de militaire dienstplicht is dat dienstweigering op grond van gewetensbezwaren niet meer overwogen hoeft te worden.

Een niet-rokengedeelte in een restaurant is net zoiets als een niet-urinerengedeelte in een zwembad.
Anthony Kedley

Voor de verzekeringstechnische consequenties van het overleven van kanker bestaat (nog) geen afdoende remedie.

Het inlassen van een kort 'middagdutje' na de lunch komt tegemoet aan een fysiologische behoefte en leidt tot een hogere activiteit en productiviteit in het verdere verloop van de dag.
Eigen waarneming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