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Improving the quality of antibiotic treatment in a Dutch hospital

I. H. Bartelink[1], R. J. M. Brüggemann[1], G. J. van Asselt[2], J. W. P. M. Overdiek[1], P. A. M. M. Boermans[1] & P. M. Oostvogel[2]
[1]Central Hospital Pharmacy The Hague, [2]Department of Medical Microbiology, Medical Centre Haaglanden, The Hague, The Netherlands

Introduction: Although antibiotic formularies have been established in many Dutch hospitals, the implementation of their guidelines has not been studied extensively. The goal of our study was to optimise the use of the antibiotic formulary in Medical Centre Haaglanden, a 777-beds hospital on two locations. This study focuses on one of these locations.

Methods: To assess quality of baseline antibiotic therapy, a pharmacist specifically assigned for this study, performed a two-month evaluation on internal medicine and surgical wards. Guidelines of the antibiotic formulary were considered as the golden standard. Criteria to judge the quality of therapy were correctness of: 1) dose, 2) route of administration, 3) length of therapy, 4) choice of antibiotics and 5) justification of the use of antibiotics. A treatment was defined as optimal when all these criteria were met. During the course of therapy the treatment was reevaluated continuously.

After assessment of the baseline, the following interventions were performed. Physicians and nurses were instructed monthly. Guidelines for an early switch from intravenous to oral antibiotic therapy were introduced. The pharmacist checked all medical charts on daily rounds. Interventions took place by giving advice in individual cases. Results of a three-month intervention period are discussed.

Results: During the baseline period, the antibiotic therapy of 77 surgical and 32 internal medicine patients was reviewed. On average, the pharmacist re-evaluated the choice of antibiotics three times during the course of treatment. On the surgical wards optimal treatment was achieved in 42% of scored therapies. The most frequent deviations were 1) choice of antibiotics (28%) and 2) route of administration (14%). On the internal medicine ward 51% of reviewed therapies met all criteria. The deviations on this ward were evenly spread. In the intervention period, 64% of scored therapies in the surgical versus 77% in the internal medicine wards were classified as optimal. All evaluated parameters improved. In both departments, deviations from the formulary were mainly caused by reluctance to use intravenous gentamicin. This could not be altered by the aforementioned interventions and influenced the outcome.

Conclusion: This study clearly shows that distributing an antibiotic formulary is not sufficient to optimise antibiotic treatment. Much effort is required to implement an antibiotic formulary to it's full extent. We have shown that significant improvement can be achieved by above-mentioned interventions. By organising consensus meetings we expect to eliminate some systematic deviations, and thus improving the results even more.

Population pharmacokinetics of nelfinavir in hiv-1-infected children

K. M. L. Crommentuyn[1], A. D. R. Huitema[1], R. P. G. van Heeswijk[2], R. A. A. Mathôt[3], H. J. Scherpbier[4], T. W. Kuijpers[4] & J. H. Beijnen[1]
[1]Slotervaart Hospital, Dept of Pharmacy & Pharmacology, the Netherlands, [2]The Ottawa Hospital, Division of Infectious Diseases, Canada, [3]Erasmus Medical Center, Dept of Clinical Pharmacy and Pharmacology, the Netherlands, [4]Emma Children's Hospital, Dept. of Pediatrics, the Netherlands

Introduction: The protease inhibitor (PI) nelfinavir (NFV) has been shown to produce a durable antiretroviral response when used in combination therapy in HIV-1 infected adults and children. NFV is available as a powder and a tablet formulation. The recommended dosage for patients aged 2 to 13 years is 20 to 30 mg/kg *tid*. Pharmacokinetics (PK) of PIs (including NFV) show high interpatient variability, especially in children. Suboptimal exposure to NFV has been correlated with virologic failure. Knowledge of the population PK of NFV in pediatric patients may be used to optimise therapy. In order to establish the PK of NFV and factors involved in the variability of therapy, a population PK analysis was performed in a cohort of HIV-1-infected children.

Methods: Patients (aged 0.1–18.7 yrs, weight 4–65 kg) were recruited from the Emma Children's Hospital, Amsterdam, the Netherlands. All participated in an ongoing open-label observational study to evaluate the efficacy and safety of triple therapy with NFV, stavudine (d4T) and lamivudine (3TC) in PI-naïve HIV-1-infected children. NFV was administered as tablets (250 mg) or as powder (50 mg/g powder) in a dose of 30 mg/kg *tid* or 45mg/kg *bid*. Population PK parameters (clearance (CL/F), volume of distribution (V/F) and absorption rate constant (K_a)) were established after log transformation of the data. Interindividual (IIV) and interoccasion variability (IOV) in the PK parameters were estimated. Residual variability was modelled with an exponential model. A number of covariates of interest were tested for inclusion in the population PK model by stepwise addition into the basis model. A decrease of 3.8 in the objective function (goodness of fit characteristic) was deemed significant ($p < 0.05$). NONMEM (Version V1.1) was used throughout.

Results: A total of 694 plasma concentrations were available, consisting of full PK curves at either *tid* or *bid* dosing (27 curves from

19 children), and of plasma concentrations at single time points. A one-compartment model with fist order absorption and elimination process and a lagtime (Tlag) best described the data. CL/F and V/F were allometrically scaled for median bodyweight (18 kg). CL/F for NFV was 33.7 L/h with an IIV and IOV of 29% and 34%, respectively. V/F for NFV was 193 L, K_a was 0.65 h^{-1} (IIV 52%) and Tlag was 0.33 h. Two covariates were found to improve the fit when added to the basic model. CL/F of NFV was correlated with age. CL/F decreased with increasing age (e.g., CL/F at age 2 is 35.9 L/h, at age 12 is 28.7 L/h ($p < 0.05$)). The NFV formulation was correlated with the bioavailability (F). F was increased with 43% (±15%) in patients who received the powder formulation ($p < 0.001$).

Conclusions and future perspectives: The PK of NFV were adequately described with the developed population model. In future studies plasma concentrations of the pharmacologically active NFV metabolite M8 will be added to the model and the influence of covariates on the PK will be further studied.

Bayesian pharmacokinetically guided dosing of paclitaxel in patients with non-small cell lung cancer

M. E. De Jonge, H. J. G. D. van Den Bongard, A. D. R. Huitema, R. A. A. Mathôt, H. Rosing, R. van Maanen, C. Koopman-Kroon, P. Baas, N. van Zandwijk, M. Keessen, S. Rodenhuis, J. H. Beijnen & J. H. M. Schellens

The Netherlands Cancer Institute and Slotervaart Hospital, Amsterdam, The Netherlands

Aim: Paclitaxel is a taxane derivative with a profound antitumour activity against a variety of solid tumours. In a previous clinical study with non-small cell lung cancer patients it was shown that patients obtaining paclitaxel plasma concentrations of 0.1 μmol/L during 15 hours or longer showed increased survival[1]. The purpose of this study was to evaluate the feasibility of Bayesian dose individualisation to attain paclitaxel plasma concentrations above this threshold concentration during 15 hours or longer.

Methods: Patients with non-small cell lung cancer were treated with paclitaxel and carboplatin for a maximum of 6 courses every 3 weeks. During the first course, the registered dose (175 mg/m^2) of paclitaxel was administered intravenously (iv) in 3 hours. Carboplatin was administered as a 30 min iv infusion in a dose calculated according to the Calvert formula with a target area under the concentration-time curve of 6 mg/ml*min. In subsequent courses, the paclitaxel dose was individualised based on observed paclitaxel concentrations in plasma during the previous course(s). A Bayesian algorithm was used to estimate individual pharmacokinetic parameters, applying a previously developed population pharmacokinetic model using the program NONMEM. The paclitaxel dose of a subsequent course was increased to the lowest dose for which the predicted time in which the paclitaxel plasma concentration exceeds 0.1 μmol/L was higher than 15 h (minimum dose 175 mg/m^2).

Results: A total of 21 patients have been included in the study (86 evaluable courses). During the first course, the time above the threshold concentration ranged from 7.6 to 31.6 hours; for 9 patients (43%) the duration of time above the threshold concentration was less than 15 hours (range 7.6–13.4 hours). During subsequent individualized courses, the time above the threshold concentration was less than 15 hours for 20%, 14%, 23%, 11% and 11% of the patients in the second, third, fourth, fifth and sixth course, respectively. Dose increments, ranging from 180 to 240 mg/m^2, were performed in 29 of the 65 individualised courses.

Toxicity was reversible and manageable and was mainly haematologic (granulocytopenia grade 3/4 in 81% of the patients).

Conclusion: The results indicate that pharmacokinetically guided dosing of paclitaxel is feasible and results in a higher percentage of patients with a duration of time that the paclitaxel concentration of 0.1 μmol/L was achieved during 15 hours or longer compared to standard dosing of the compound.

1 Huizing MT et al. J Clin Oncol 1997; 15: 317–29.

Cardioversion of atrial fibrillation with a loading dose of flecainide tablets or an oral solution of a mixture of flecainide and cisapride

V. H. M. Deneer[1], J. H. Kingma[2], L. Lie-A-Huen[1], J. H. Proost[3], N. M. van Hemel[2], G. M. M. Uytdehaag[4], P. H. J. M. Dunselman[4], A. Stuurman[5] & J. R. B. J. Brouwers[6]

[1]Dept of Clinical Pharmacy, [2]Dept of Cardiology, St Antonius Hospital, Nieuwegein, [3]GUIDE, Section Pharmacokinetics and Drug Delivery, [4]Dept of Cardiology, [5]Dept of Clinical Pharmacy, Amphia Hospital, Breda, [6]Section Pharmacotherapy, Groningen

Introduction: An oral loading dose of flecainide could be convenient both for patients with an episode of atrial fibrillation (AF) admitted to outpatient departments or for episodic treatment of AF by self administration outside the hospital.

Objectives: To study the pharmacodynamics and pharmacokinetics of two oral formulations of flecainide in patients with an episode of AF.

Methods: Patients with AF were randomised, after stratification by the duration of AF, to receive 3 flecainide tablets of 100 mg or an oral solution containing 300 mg of flecainide and 20 mg of cisapride. Blood samples were collected and 12-lead electrocardiograms (ECG) were obtained at sampling times. The treatment was considered successful if sinus rhythm (SR) occurred within 5 h. The proportion of patients with SR was calculated by the Kaplan-Meier method. The treatment groups were compared by using the Log Rank Test. The maximum flecainide serum concentration (Cmax), the corresponding time (Tmax), the absorption rate constant (ka), the lag-time (tlag) and the area under the curve (AUC) were calculated. Logistic regression was used to study factors associated with cardioversion.

Results: Sixty four patients were randomised. Seven patients converted to SR before ingestion of flecainide and 3 patients were wrongly included. SR was restored in 17 of 27 patients (63%) in the oral solution group versus 12 of 27 patients (44%) in the tablets group ($P = 0.14$). If AF lasted <24 h 15 of 17 patients (88%) treated with the oral solution converted to SR, while in 8 of 16 patients (50%) treated with tablets cardioversion occurred ($P = 0.023$). Pharmacokinetic and ECG parameters are shown in Table 1. A duration of AF <24 h (OR 6.34; 95% CI 1.70–23.73) and a higher ka (OR 1.20 per unit of 0.1 h^{-1}; 95% CI: 1.01–1.44) were associated with

Table 1
Pharmacokinetic and ECG parameters

	Oral solution	Tablets	P value
Cmax (mg/l)	0.60 ± 0.17	0.43 ± 0.14	0.0002
Tmax (h)	1.05 ± 0.71	2.37 ± 1.20	<0.0001
ka (h^{-1})	0.97 ± 0.43	0.48 ± 0.24	<0.0001
tlag (h)	0.30 ± 0.16	0.36 ± 0.19	NS
AUC4h (mg h/l)	1.72 ± 0.52	1.31 ± 0.42	0.003
max QRS (ms)	112 ± 15	112 ± 19	NS
max QTc (ms)	406 ± 18	420 ± 17	NS

Mean values ± SD, QTc interval: during SR in patients without QTc prolonging drugs.

cardioversion. Other patient characteristics, pharmacokinetic or ECG parameters did not increase the probability of SR. No serious arrhythmias were observed.

Conclusions: The probability of cardioversion after oral loading dosing of flecainide in patients with AF is dependent on ka. Rapid loading of the effect compartment, i.e. the atria, appears to be critical to reach cardioversion.

Patient, doctor, and organisational factors affecting hypertension management in patients with type 2 diabetes

P. Denig, C. F. Schaars, W. N. Kasje &
F. M. Haaijer-Ruskamp
Department of Clinical Pharmacology, University of Groningen, The Netherlands

Introduction: Tight blood pressure control significantly reduces morbidity and mortality in diabetic patients, but current hypertension management seems far from optimal. To develop efficient intervention strategies insight is needed in the specific factors that affect the quality and outcome of care.

Objective: We aimed to assess the quality of hypertension care in patients with type 2 diabetes and to identify patient, physician and organisational factors associated with suboptimal care in general practice.

Methods: Analysis of process and outcome measures, including check of blood pressure in the previous year, treatment of hypertension, and achievement of target blood pressure levels. ACE-inhibitors were considered as the optimal treatment for patients with a recorded diagnosis of hypertension or with average blood pressure levels above 135/85 mm Hg. Data from 895 randomly selected diabetic patients were extracted from the computerised medical records of 95 general practitioners (GPs). A short survey was used to collect additional physician and organisational characteristics.

Results: For 652 of the 895 patients (73%) one or more blood pressure measurements were recorded in the last year. Of these patients only 132 (20%) reached a target level of 135/85 mm Hg. In total, 595 patients were classified as having hypertension, 192 of whom received no treatment (32%), 193 received treatment with an ACE-inhibitor (32%), and 210 received other antihypertensives. Patients visiting a special diabetic service, being recently referred to a specialist, or being overweight had better recordings of their blood pressure. Suboptimal treatment was higher in older patients and smoking patients. Treatment was better in patients with coronary comorbidity or being recently referred to a specialist. Not achieving the blood pressure target was related to older age of the patients. Characteristics such as the GP's working experience, or type and size of the practice were not associated with the quality of hypertension care.

Conclusion: Interventions aimed at improving the quality of hypertension management in diabetic patients should focus more on specific patients groups than on specific doctors.

Determination of alcohol infusion rate by clamping of breath alcohol concentration – a comparison with modelled infusion regimens based on individual pharmacokinetics

G. J. H. Dumont, B. J. Oosterink, S. Paltansing,
N. van Burgel, M. van Der Linden, R. Schoemaker &
J. M. A. van Gerven
Centre for Human Drug Research, Leiden

Introduction: Ethanol has profound physiological and psychological effects, which are usually concentration-dependent. Therefore, EtOH effects or drug-EtOH interactions are preferably studied at steady state EtOH-levels. To achieve a steady state EtOH plasma level, various methods are used, which usually produce adequate average but variable individual EtOH profiles. A recent algorithm includes on-line adaptation of EtOH infusion rates based on concomitant changes in breath alcohol (BrAC).[1] This method entails oral loading followed by intravenous infusion. It has not been widely applied.

Objectives: The clamping method was adapted, using intravenous EtOH only, and an on-line spreadsheet procedure to guide dosing. This was compared to a 'two-step prekinetic procedure', where pseudo-steady-state infusion was based on pre-study-day determination of EtOH kinetics in participants.

Methods: This was an unblinded study in healthy subjects, which consisted of two parallel designs:

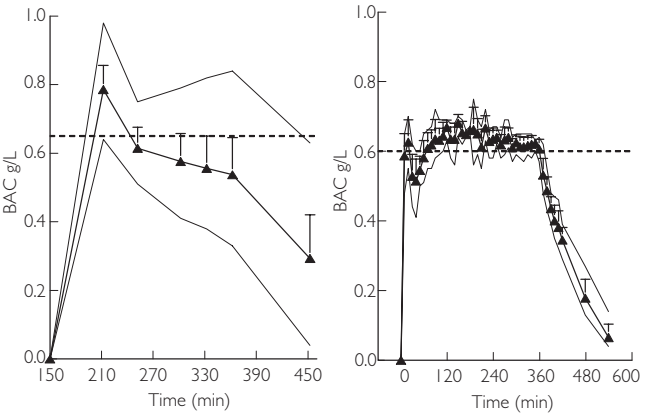
A '*two-step prekinetic procedure*' started with individually determined EtOH dispositions during a pre-study occasion. Fifty grams of EtOH in (10% in glucose 5%) were infused over 1 hour. Breath-

and serum EtOH levels were measured at 0, 30, 55, 75, 90, 120, 180, 240, 300 and 360 min. Empirical Bayes' estimates of kinetic parameters were then used to simulate individual infusion regimens aimed to maintain pseudo-steady-state-levels of 0.65 g/L. Regimens consisted of a constant infusion over 1 hour (loading phase) followed by a lower constant rate infusion over 3 hours (maintenance phase).

The '*ethanol clamping procedure*' started with an EtOH loading phase. After the first six subjects, this was adapted to infusion of 72 g for 10 min followed by 36 g for 10 min. This loading phase was followed by a clamping phase, targeted at 0.6 g/L. Using a simple spreadsheet, the change in BrAC in the previous 10 min measurement interval was plotted dynamically, against the concomitant infusion rate. This produced an increasingly stable trend line with a regression equation, which was used to determine the infusion speed for the next 10 min, by plotting the desired BrAC-change (leading to the target BrAC) in the equation.

Results: The average EtOH profiles for the two procedures are shown in the graph (left: 'two-step', right: 'clamping').

Conclusions: Clamping of BrAC results in far more accurate EtOH-levels than infusion based on PK-modelling.



1 O'Connor, S. et al. Alcohol Clin Exp Res 1998; 22(1): 202–10.

Teaching resource centre (TRC): teaching clinical pharmacology in an integrated medical school curriculum

K. L. Franson[1,2], E. A. Dubois[1,2], J. M. A. van Gerven[1,2], F. Cornet[1], J. H. Bolk[2] & A. F. Cohen[1,2]

[1]Centre for Human Drug Research, [2]Leiden University Medical Center

Introduction: Medical professionals are increasingly confronted with new medicines, rising costs of therapy, and an increasing number of drug misadventures. It is reasonable to assume that increased knowledge about drugs will increase the quality of drug use. The TRC provides the LUMC medical students with pharmacological knowledge based in pathophysiology. Thus, students can see the relevance of a pharmacological mechanism for a particular disease state.

Methods: We first determined 5 ability outcomes:
Upon completion of the curriculum, students can:

1. explain pharmacological mechanisms of action;
2. explain physiological/pathophysiological mechanisms of disease;
3. critically analyse indications for drugs by comparing pharmacological and pathophysiological mechanisms;
4. select drug therapy based on pharmacotherapeutic principles;
5. monitor drug therapy based on pharmacotherapeutic principles.

Then provided the students with several learning opportunities for practicing these outcomes, including using the TRC Pharmacology computer program and writing the Patient Evaluation and Plan.

TRC Pharmacology computer program (TRCP): Using a newly developed graphical language for uniformity, a self-study computer database program was created[1]. The TRCP program contains graphical material, supportive text and charts, and formative feedback questions as instruction for outcomes 1 & 2, as the material is presented in a treeview with links starting with physiology and proceeding through pathophysiology to pharmacology mechanisms.

Patient Evaluation and Plan (PEP): PEP provides students with a standardized format for therapeutic decision making and communicating a therapeutic plan (Outcomes 3, 4 & 5). Students are provided opportunities to practice PEP writing via an online example case that introduces the PEP process in an interactive step-by-step manner. Subsequent cases and plans are emailed into a central location for assessment.

Evaluation: The progress of incorporating the outcomes into the curriculum is being catalogued. The table below shows the percentages of blocks which adopted the outcomes:

Outcome	2001–2002	2002–2003
1	51.4	60.7
2	53.3	59.3
3	15	50
4	14	47.1
5	0	52.9

Student evaluations are positive regarding learning strategies and indicate a preference for higher level assessments and integration. Next year is expected to yield a higher percentage of pharmacology outcomes throughout the curriculum.

Conclusions: This process is increasingly being adopted as the method of providing pharmacology education in the LUMC curriculum. Intial use was limited to the more basic knowledge outcomes, but now incorporates the application of knowledge.

1 British Journal of Clinical Pharmacology 2001; 52: 623–4.

Trends in antihypertensive drug prescribing in dutch general practice from 1996 to 2000

J. P. Greving[1], P. Denig[1], W. J. van Der Veen[2], F. W. Beltman[2], M. C. J. M. Sturkenboom[3] & F. M. Haaijer-Ruskamp[1]
[1]Clinical Pharmacology, University of Groningen, the Netherlands, [2]General Medicine, University of Groningen, the Netherlands, [3]Medical Informatics, Erasmus MC Rotterdam, the Netherlands

Introduction: The use of newer antihypertensives, ACE-inhibitors and A-II-antagonists, has increased considerably in the last decade. It is unclear to what extent this increase is justified in hypertensive patients in view of possible comorbidities such as heart failure or diabetes.

Objectives: To examine trends in the overall and initial treatment of hypertension, and to assess the relation with comorbidity in general practice from 1996 to 2000 in the Netherlands.

Methods: We conducted a retrospective cohort study using data from the Integrated Primary Care Information database. The source population consisted of a dynamic cohort of 27317 persons with a diagnosis of hypertension and at least 6 months valid electronic medical record history. We estimated the point prevalence of overall antihypertensive drug by calendar year by considering as users all persons with a prescription for an antihypertensive drug in the 6 months prior to the prevalence date (first Wednesday in October).

As initial treatment we considered the first prescription of an antihypertensive drug within a year after the diagnosis of hypertension. Separate calculations were made for subpopulations of patients with a comorbidity of diabetes, heart failure or angina.

Results: From 1996 to 2000, overall antihypertensive drug use increased from 65% to 71% in all patients with hypertension. In this population there were increases in the use of diuretics (from 26% to 30%), beta-blockers (from 25% to 30%), A-II-antagonists (from 1% to 8%), but ACE-inhibitor use remained stable (21%). In hypertension patients with heart failure ACE-inhibitors were prescribed more frequently (27%), and also no increase in prescribing was found. In hypertension patients with diabetes ACE-inhibitor use increased (from 26% to 32%). Increases in the use of A-II-antagonists did not differ in the various subpopulations. Regarding initial treatment, the proportion of patients starting on A-II-antagonists increased (from 4 to 11%), and on ACE-inhibitors remained almost stable (from 23 to 21%). Initial treatment with diuretics or beta-blockers remained just over 50% during the whole study period.

Conclusion: The use of ACE-inhibitors for hypertension is partly related to comorbidities for which their use is desirable. The increase in the use of A-II-antagonists is not confined to specific subpopulations for which their use might be more warranted.

Tacrolimus, but not cyclosporine, dose requirement is correlated with CYP3A5*3 and CYP3A4*1B genotype

D. A. Hesselink[1], R. H. N. van Schaik[2], P. J. H. Smak Gregoor[1], W. Weimar[1] & T. van Gelder[1,3]
Departments of [1]Internal Medicine, [2]Clinical Chemistry and [3]Pharmacy, Erasmus MC, Rotterdam, The Netherlands

Introduction: The calcineurin inhibitors (CNI) cyclosporine A (CsA) and tacrolimus (TRL) are standard immunosuppressive drugs in many transplantation centers. However, both drugs have a narrow therapeutic index and show considerable interindividual variation in their pharmacokinetics (PK). Therefore, therapeutic drug monitoring is essential to avoid over -or underimmunosuppression. The poor oral bioavailability of CNI is thought to result from the actions of the main CNI metabolizing enzymes CYP3A4 and CYP3A5 and the multi-drug efflux pump, P-gp, encoded by the *MDR1* gene. Recently identified genetic polymorphisms of these 3 enzymes could explain the observed interindividual variability in CNI PK.

Aim: To determine the role of genetic polymorphisms in *CYP3A4*, *CYP3A5* and *MDR-1* with respect to interindividual variability in CsA and TRL PK.

Methods: Kidney transplant patients receiving CsA (n = 110) or TRL (n = 64) were genotyped for *CYP3A5*3* and *6* (Kuehl 2001), *CYP3A4*1B* (Rebbeck 1998) and *MDR-1 C3435T* (Hoffmeyer 2000). CsA and TRL concentrations were analysed in whole blood using the EMIT 2000 assay at 3 and 12 months after transplantation. Dose-adjusted pre-dose (C0) concentrations were calculated and correlated with genotype.

Results: TRL dose-adjusted C0 was significantly higher in *CYP3A5 *3/*3* patients (n = 45 or 73%) when compared to **1/*3* plus **1/*1* (wild-type) patients (n = 17 or 27%): Median (range): 94 (34–398) vs. 61 (37–163) ng/ml per mg/kg; $p < 0.0001$, Mann-Whitney U test. *CYP3A4*1B* allele carriers (n = 10 or 16%) showed a significantly lower TRL dose-adjusted C0 compared to patients with the wildtype (**1/*1*) genotype (n = 54 or 84%): Median (range): 57 (40–163) vs. 89 (34–398) ng/ml per mg/kg; $p < 0.003$, Mann Whitney U test. No evidence was found supporting a role for the *MDR-1 C3435T* polymorphism in TRL PK. For CsA, none of the 3 polymorphisms studied correlated with dose requirement.

Conclusion: CYP3A5 genotype is strongly correlated with TRL dose requirement. Patients with the *CYP3A5*3/*3* genotype need less TRL to reach target concentrations compared to *CYP3A5*1* allele carriers and may have a higher likelihood of reaching toxic drug concentrations. *CYP3A4*1B* carriers need more TRL to reach target C0 compared to the *CYP3A4*1* carriers and may therefore be at risk of developing acute rejection.

1 Hoffmeyer S, et al. Proc Natl Acad Sci USA 2000; 97: 3473.
2 Kuehl P, et al. Nat Genet 2001; 27: 383.
3 Rebbeck T, et al. J Natl Cancer Inst 1998; 90: 1225.

A Phase I, randomized, open-label, parallel-cohort, dose-finding study of elacridar (GF 120918) in combination with 2.0 mg oral topotecan in cancer patients

I. E. L. M. Kuppens[1], S. Radema[2], H. Rosing[1], E. Stokvis[1], M. Swart[1], R. C. Jewell[3], M. Russo[4], A. Karakus[2], E. Witteveen[2], J. H. Beijnen[1], E. Voest[2] & J. H. M. Schellens[1]

[1]The Netherlands Cancer Institute, Amsterdam, NL, [2]University Medical Centre, Utrecht, NL, [3&4]GSK, RTP, NC and Philadelphia, PA, USA

Introduction: Increasing oral bioavailability (F) of topotecan, a substrate for the drug efflux proteins BCRP and P-gp, may result in greater tolerability and may permit prolonged oral administration. Elacridar is a potent inhibitor of Breast Cancer Resistance Protein and P-glycoprotein. Inhibition of these proteins significantly increases F (Kruijtzer *et al*., 2002).

Objectives: The main goals of this study were to determine the minimum dose of elacridar required for maximum oral F of topotecan and to determine the appropriate schedule of co-administration of oral topotecan and elacridar. Furthermore, safety and tolerability of this combination and inter-patient variability of the PK of oral topotecan plus elacridar as compared to iv topotecan alone were studied.

Methods: twenty patients were randomized to receive 100, 300, 500, 700 or 1000 mg elacridar with 2 mg oral topotecan and to either simultaneous administration of oral topotecan and elacridar or to elacridar 60 min prior to oral topotecan, on day 1 or 8 of study. Patients received iv topotecan on days 15–19 (2.0 mg on day 15, 1.5 mg/m^2 on day 16–19). This was followed by 1.5 mg/m^2/d * 5 d, every 21 d standard treatment. Blood samples were collected on day 1, 8 and 15. Elacridar plasma levels were determined by a HPLC-MS method. Plasma topotecan lactone and topotecan total (lactone and carboxylate) levels were determined by a validated HPLC method.

	Total 'F' (= po/iv)		Lactone 'F' (= po/iv)	
	0 min	60 min	0 min	60 min
N	13	13	10	11
mean	1.10	1.05	1.08	1.05
SD	0.14	0.13	0.10	0.14
%CV	12	12	9	14
range	0.91–1.34	0.85–1.33	0.93–1.22	0.76–1.28

Results: PK interim analysis has been performed. There was no significant effect on the dose of elacridar on the F of oral topotecan over the studied dose-range of 100–1000 mg. All patients tolerated combination of elacridar and topotecan very well. A total of 15 serious adverse events have been reported, of which two were considered drug-related (febrile neutropenia and hemoptysis with thrombocytopenia). Both events occurred during cycles of d*5 iv topotecan therapy.

Conclusion: Administration of 100 mg elacridar and oral topotecan results in complete apparent bioavailability of oral topotecan. Furthermore co-administration of elacridar and oral topotecan is as effective as when elacridar is given 60 min prior to topotecan. Elacridar combined with oral topotecan is well tolerated. In future studies, a dose of 100 mg elacridar is adequate to optimise oral bioavailability of oral topotecan.

Kruijtzer, et al. J Clin Oncol 2002; 20(13): 2943–50.

Oral bioavailability of docetaxel in combination with OC 144-093 (ONT-093)

I. E. L. M. Kuppens[1], M. J. van Maanen[2], H. Rosing[2], T. M. Bosch[2], A. Fitzpatrick[3], J. H. Beijnen[1,2] & J. H. M. Schellens[1]

[1]The Netherlands Cancer Institute, Amsterdam, NL, [2]Slotervaarthospital, Amsterdam, NL, [3]Elan Pharmaceutical Technologies, Ireland

Introduction: Docetaxel has a poor bioavailability (F) when given orally to man. It is a substrate with high affinity for the MDR1 efflux protein P-glycoprotein (P-gp). High expression of P-gp combined with high affinity of docetaxel for the efflux pump is the most plausible explanation for the low systemic availability upon oral administration. Combination of docetaxel with OC 144-093, a selective and potent P-gp inhibitor may increase oral F of docetaxel.

Objective: This phase I study was designed to explore the systemic exposure of docetaxel after combined single oral administration of docetaxel and OC 144-093 and after a single iv dose of docetaxel alone. Furthermore the safety of combined treatment was determined and it was explored whether genetic polymorphisms of the MDR1 gene are associated with variability in docetaxel pharmacokinetics.

Methods: Twelve patients were randomised and received docetaxel on two occasions. In treatment arm A patients received 500 mg OC 144-093 po followed 30 min later by 100 mg docetaxel po, administered in the iv formulation as Taxotere®. This time interval was altered, after examination of the plasma docetaxel levels of the first four patients, to intake at the same time.

Two weeks later patients received 100 mg docetaxel iv as a 1 hour infusion, without OC 144-093. In treatment arm B patients received the same treatment vice versa. Toxicity was evaluated every course. MDR1 polymorphisms in exon 12 (C1236T), exon 21 (G2677T) and exon 26 (C3435T) were determined (by PCR and sequencing). Plasma concentrations were determined by validated HPLC methods. PK analysis was performed using WINNONLIN^{TM} version 3.0.

Results: Three patients (25%) developed a drug-related SAE. The toxicities were all CTC-grade 3 except for neutropenia (grade 4) combined with fever. The two other related SAE's were diarrhea combined with rectal blood loss and fever with malaise. Docetaxel 100 mg iv generates higher C_{max} and AUC_{0-48} values compared to docetaxel po combined with OC 144-093 ($p = 0.001$ and $p = 0.012$). C_{max} values are 415 ± 255 (po) and 2126 ± 1010 ng/ml (iv). AUC_{0-48} values are 844 ± 718 (po) and 2571 ± 1530 ng.h/ml (iv). The 'apparent F' was 0.33 ± 0.28 and %CV was 86%. One patient had a homozygous 3435T/T mutation, which is associated with low intestinal P-gp expression (and was also homozygous for mutations in exon 21 and 12).

Conclusion: Large intra and interpatient PK variation was found. Higher plasma levels were observed after iv docetaxel compared with docetaxel po plus OC 144-093. More patients should be evaluated to determine the effect of P-gp single nucleotide polymorphism's on PK values.

The effectiveness of HMG-COA reductase inhibitors is affected by ACE insertion deletion polymorphism

A. H. Maitland-Van Der Zee[1,2], B. H. Ch Stricker[2], O. H. Klungel[1], J. J. P. Kastelein[3], A. Hofman[2], J. C. M. Witteman[2], H. G. M. Leufkens[1], C. M. van Duijn[2] & A. De Boer[1]
[1]Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands, [2]Department of Epidemiology & Biostatistics, Erasmus University Medical Centre, Rotterdam, The Netherlands, [3]Department of Vascular Medicine. Academic Medical Center, Amsterdam, The Netherlands

Introduction: Inconsistent results have been published on the effects of pravastatin on angiographically defined coronary atherosclerosis in subjects with different ACE genotypes.

Aim: To assess whether the effectiveness of statins in the prevention coronary heart disease and total mortality is influenced by ACE Insertion (I)/Deletion (D) polymorphism in an elderly population.

Methods: We used data from the Rotterdam study, a prospective population-based cohort study in the Netherlands, which started in 1990 and included 7983 subjects of 55 years and older. Subjects treated with cholesterol lowering drugs at baseline or a baseline total cholesterol ≥6.5 mmol/l were included. We compared the incidence of the 4 outcomes total mortality, all coronary heart disease (CHD), ischemic heart disease (IHD), and all coronary mortality in subjects who received ≥2 years of statin treatment with the incidence in untreated subjects by using a Cox proportional hazard model with cumulative statin use defined as time dependent covariates. Follow-up was available until 1-1-2000. Analyses were stratified according to ACE genotypes. All relative risks were adjusted for age, sex, diabetes mellitus, systolic blood pressure, bmi, total cholesterol, HDL cholesterol, history of cardiovascular disease, family history of mi, current smoking, use of coumarins and platelet inhibiting salicylates.

Results: The adjusted relative risk (RR) mortality from any cause was 0.65 [95% CI: 0.44–0.95] and of all coronary events 0.81 [95% CI: 0.55–1.19] for subjects treated with statins for ≥2 years compared with untreated subjects. In subjects with the DD genotype the RR of developing a coronary event was 1.29 [95% CI 0.62–2.69], in subjects with the ID genotype the RR was 0.87 [95% CI 0.52–1.45], while in subjects with the II genotype the RR was 0.40 [95% CI 0.15–1.10]. Synergy indices are shown in table 1.

Conclusions: In male subjects with the DD genotype statins did not reduce the risk of all coronary disease and this lack of effect was significantly different from patients with the II genotype in which the risk reducion of statins was observed. There was no interaction between statins and ACE genotype on total mortality.

Table 1
Synergy indices for DD against II

	All SI*	Male SI*	Female SI*
Total mortality	1.2 (0.4–3.6)	2.6 (0.6–10.9)	0.4 (0.1–2.4)
All CHD	2.7 (0.9–8.6)	7.4 (1.2–46.8)	1.3 (0.3–6.0)
IHD	3.1 (0.7–13.3)	NA	NA
Coronary mortality	3.2 (0.6–17.7)	NA	NA

**Adjusted.*
NA: not applicable because of low numbers.

Determinants of persistence with statin use in daily medical practice

A. K. Mantel-Teeuwisse[1], W. G. Goettsch[2], O. H. Klungel[1], A. De Boer[1] & R. M. C. Herings[2]
[1]Utrecht Institute for Pharmaceutical Sciences (UIPS), Dept. of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, The Netherlands, [2]PHARMO Institute, Utrecht, The Netherlands

Background: Persistence with lipid lowering drug use is important to gain full treatment benefit. Persistence with statins has been studied in the elderly, but data from the general population is limited.

Aim: To assess persistence with statin use, and to identify factors affecting persistence in the general population.

Methods: Data were obtained from the PHARMO database including linked pharmacy records and hospital discharge records of 865,000 subjects in The Netherlands. In the period 1996–2001, all new users of statins, defined as patients not receiving any statin for at least two years before the first dispensing of a statin, were extracted.

Episodes of statin use were constructed for each patient according to Catalan *et al.*, 2000. In case of interruptions between two prescriptions of <45 days, the episode was considered uninterrupted. We assessed persistence after one and after two years of treatment. Persons were considered to be persistent if they had a treatment episode of at least 365 and 730 days, respectively.

Additionally, the association between determinants and failure to persist (until two years) was assessed using Cox proportional hazard analysis.

Results: A total of 8335 starters of statins were selected.

Persistence with use at one year was 63.7% (95% confidence interval [CI] 62.7%–64.8%) for all statins, and decreased to 48.5% (95% CI 47.4%–49.6%) at two years.

Factors predicting failure to persist included older age (Relative risk [RR] 0.84; 95% CI 0.76–0.93 for those aged 45–64 years compared with those <45 years, and RR = 0.82; 95% CI 0.74–0.91 for those >65 years compared with those <45 years), a history of anti-

hypertensive drug use (RR = 0.91; 95% CI 0.85–0.98), psychotropic drug use (RR = 1.13; 95% CI 1.06–1.20), or a hospital admission for ischaemic heart disease in two years previous to the start of statin treatment (RR = 0.78; 95% CI 0.70–0.88). There was no difference in persistence according to gender.

Compared to starters with simvastatin, the risk of discontinuation was lower for atorvastatin (RR = 0.90; 95% CI 0.83–0.96), similar for pravastatin (RR = 0.99; 95% CI 0.91–1.08), and higher for fluvastatin (RR = 1.27; 95% CI 1.12–1.39).

Conclusions: Persistence with statin use declined over time. Factors affecting persistence included age, previous use of antihypertensive or psychotropic drugs, a history of ischaemic heart disease and type of statin.

Catalan VS, et al. Value in Health 2000; 3: 417–26.

Nasal drug delivery to the cerebrospinal fluid: transport of a hydrophilic drug

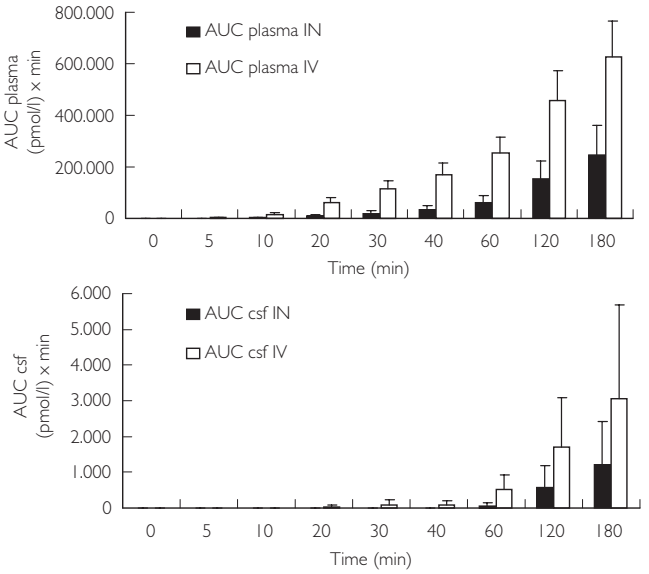
P. Merkus, H. J. Guchelaar[1], D. A. Bosch[2] & F. W. H. M. Merkus[3]

Dept of Otorhinolaryngology, [1]Dept of Clinical Pharmacy, [2]Dept of Neurosurgery, Amsterdam Medical Center, University of Amsterdam and the, [3]Center for Bio-Pharmaceutical Sciences, University of Leiden, The Netherlands

Aim: The aim of this study was to investigate the possibility of direct transport of drugs from the olfactory area to the cerebrospinal fluid (CSF) by intranasal administration (IN) of a hydrophilic drug in human volunteers. In a large number of animal studies evidence has been found for drug transport via the nose to the brain [1]. A recent human study with neuropeptides suggests such a transport [2], but real proof comparing CSF levels after IN and after intravenous administration (IV) is missing.

This study evaluates drug CSF levels in patients at the neurosurgery department after IN and IV administration of hydroxocobalamin, used in this study as a hydrophilic model compound. It has been chosen because of safety (vit. B12 analogue) and good nasal absorption [3].

Methods: We recruited five patients from the Neurosurgery department with an external cerebrospinal drain. Each patient received on the first day hydroxocobalamin IN in a dose of 1500 µg (750 µg in each nostril) and the second day 75 µg IV. Blood samples and CSF samples were collected just before and at 5, 10, 20, 30, 40, 60, 120 and 180 minutes after drug administration. Cobalamin levels were measured with a radioimmunoassay method. Concentration-time curves of the plasma and CSF levels of cobalamin were compared after IN and IV administration.



Results and discussion: The mean AUC_{CSF}: AUC_{PLASMA} ratio of cobalamin (0–180 min) after IN and after IV administration were similar (0.0049), which indicates no additional transport of the drug from nose to CSF. The uptake of the drug in the CSF follows the same pattern (see figure) as the uptake in blood after IN and IV with a lag time of about 30 minutes. It seems plausible that this is the time needed to pass the blood-brain barrier.

1 Mathison S, et al. J Drug Targ 1998; 5: 415–41.
2 Born J, et al. Nat Neurosci 2002; 5: 514–16.
3 Asselt van DZB, et al. Br J Clin Pharmacol 1998; 45: 83–6.

When are antimicrobial treatment guidelines not followed?

P. G. M. Mol[1,2], P. Denig[1], P. V. Nannan Panday[1,2], R. O. B. Gans[4], J. E. Degener[3], M. Laseur[2] & F. M. Haaijer-Ruskamp[1]

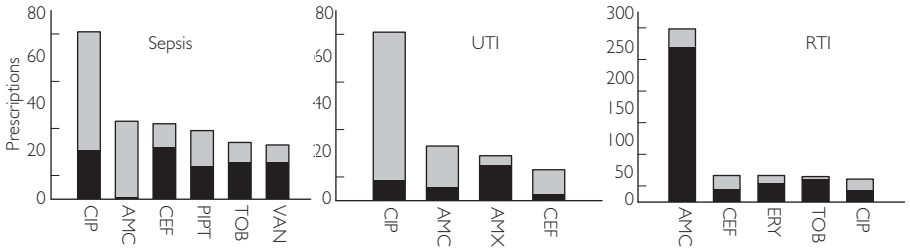
[1]Department of Clinical Pharmacology, University Groningen, [2]Pharmacy Department, [3]Department of Clinical Microbiology, [4]Department of Internal Medicine, [2,3,4]at University Hospital Groningen, the Netherlands

Introduction: In an era of increasing bacterial resistance and the availability of a plethora of antimicrobial agents hospitals develop policies to promote prudent antimicrobial prescribing. The mainstay of such policies is often an antimicrobial treatment guideline based on national and international evidence-based guidelines, on local resistance patterns and cost-effective drug choices. Adherence to antimicrobial treatment guidelines is often only moderate. The first step in improving adherence is the identification of specific problem areas in order to target the intervention. One may expect that certain patient characteristics could lead to 'rational' non-adherence.

Objective: The aim of this study is to identify relevant patient characteristics and choice of antimicrobial agents to prepare a targeted intervention.

Methods: Prescribing data were prospectively collected for patients admitted to the internal medicine department of our hospital from February 2001–February 2002 with sepsis, urinary tract infections (UTI), or respiratory tract infections (RTI). Respectively 303, 180 and 595 prescriptions for these indications were issued. The outcome variable, adherence to the guideline, was assessed by an independent observer (PVNP) for every prescription taking into account focus of the infection, aetiology, and co-morbidity as well as culture results when available. *In-vitro* test results overruled guideline recommendations if cultured pathogens were insensitive to recommended

Figure 1.
Adherence of most commonly prescribed antimicrobial. Adherent (■), non-adherent (▩).



$ Antimicrobial agents prescribed in 70% of all cases for sepsis, UTi and RTI. Cip: ciprofloxacin; AMC: amoxicillin/clavulanic acid; CEF: ceftriaxon; PIPT: piperacillin/tazobactam; TOB: tobramycin; VAN: vancomycin; AMX: amoxycillin; ERY: erythromycin

agents. The guideline recommends for empirical treatment of sepsis and RTI mainly broad-spectrum antibiotics. When *in-vitro* culture results become available the guideline recommends narrowing-down initial broad-spectrum therapy. For UTI, where most cases are uncomplicated UTI's, mostly narrow-spectrum antibiotics are recommended. The comorbidities included in the analysis were: diabetes, alcohol/drug abuse, chronic renal / hepatic failure, immunosuppressive therapy, COPD, CHF, CVA, urinary catheter of IV-drains in situ. Disease-severity was indicated by temp >38.5°C, CRP >100 mg/L-, ASAT >60 U/L-, ALAT >80 U/L-, and creatinine >130 mg/L, leucocytes >12 or <4 .352 10^9/L, longer hospital stay (>11 days) and mortality. Logistic regression was used to analyse the impact of disease-severity and comorbidity on adherence.

Results: Adherence varied from 37% for UTI, 53% for sepsis to 75% for RTI. Availability of culture results led to less adherence for RTI (OR: 0.5 [0.34–0.77]) and more adherence in UTI (OR: 3.24 [1.59–6.63]). No relation was found between disease-severity or co-morbidity and adherence to the hospital guideline in any of the infections studied. The most prescribed drug was the broad-spectrum antibiotic ciprofloxacin for UTI (39%) and sepsis (24%) and co-amoxiclav for RTI (46%). This drug-choice was mostly not adherent in case of UTI and sepsis, but adherent in case of RTI (adherence respectively 13%, 29% and 90%). [figure 1]

Conclusion: Doctors seem to choose routinely a broad-spectrum antibiotic in the three infections included in this study, irrespective of patient-characteristics. This leads to low adherence in the treatment of infections for which narrow-spectrum antibiotics are recommended and high adherence when a broad-spectrum antibiotic is the recommended treatment. These findings indicate that an intervention should target the narrowing of antimicrobial choice and not specific patient characteristics.

Academic fluoroquinolone prescribing, resistance and impact of guidelines

P. G. M. Mol[1,2], P. V. Nannan Panday[1,2], J. E. Degener[3], T. S. van Der Werf[4], F. M. Haaijer-Ruskamp[1] & R. O. B. Gans[4]

[1]Department of Clinical Pharmacology, University Groningen, [2]Pharmacy Department, [3]Department of Clinical Microbiology, [4]Department of Internal Medicine, [2,3,4]of University Hospital Groningen, the Netherlands

Introduction: Excessive ciprofloxacin use has recently been linked with the emergence of drug-resistant organisms like vancomycin-resistant enterococci. In our university teaching hospital, we observed over the past twelve years an increase in ciprofloxacin prescriptions that was mirrored by an emergence of drug-resistant enterobacteriacaeae.

Objective: The aim of this study was the effectiveness of guideline-recommended antimicrobials compared to ciprofloxacin for empirical treatment of infectious diseases. The guideline recommended ciprofloxacin only for empirical treatment of urosepsis in the presence of a catheter (combined with amoxicillin), septic-enteritis or sepsis with an ulcus as focus (combined with clindamycin), acute pyelonephritis or prostatis and invasive acute gastro-enteritis and enterocolitis. Ciprofloxacin had a limited place for culture-targeted treatment of *salmonella* species and *L. pneumophila* for these indications.

Methods: Prescribing data were collected for 795 patients (1822 antimicrobial prescriptions) admitted to the various sub-departments of the internal medicine; pulmonology, hematology, kidney-disease, gastro-enterology, general internal medicine and intensive care from February 2001–February 2002 with an infectious disease in our hospital. An independent observer assessed adherence of every prescription.

Results: Of 144 patients treated with ciprofloxacin only 32% were treated in accordance with the guideline. The case-mix comprised mainly patients with sepsis, urinary tract infections (UTI), respiratory tract infections (RTI), gastro-enteritis. Empirical therapy with ciprofloxacin was more adherent than culture-targeted therapy in all infections included [table 1] Non-adherent treatment was usually too broad (79 patients). Non-adherent treatment did not cover expected pathogens (empirical therapy) or cultured pathogens in 14 respectively 5 patients.

Table 1
Patients treated with ciprofloxacin (% adherent to guideline-recommendations)

	Empirical	Culture-targeted	Total
Sepsis	25 (40%)	15 (20%)	40 (33%)
UTI	29 (14%)	28 (3%)	57 (13%)
RTI	11 (45%)	13 (11%)	24 (50%)
Gastro-enteritis	6 (100%)	3 (67%)	9 (89%)
Other	11 (45%)	3 (33%)	14 (43%)
Total	82 (37%)	62 (26%)	144 (32%)

The leading principle in treating infectious-diseases is to start broad and later narrow-down therapy when *in-vitro* culture results become available. We reassessed antimicrobial therapy for 41 empirically treated patients where pathogens were cultured from the appropriate test-material. Guideline-recommended antimicrobial agents were equally effective (78%) as ciprofloxacin (66%) judged by *in-vitro* sensitivity testing of finally cultured pathogens. [table 2] These guideline recommended agents were frequently less broad-spectrum agents, e.g. amoxicillin or nitrofurantoin. Even with culture results available, in five patients therapy with ciprofloxacin was started that did not cover the cultured pathogens.

Conclusion: Cultured pathogens are well covered by guideline-recommended antimicrobial agents, therefore no reason exists to deviate from guideline-recommendations. In our hospital antimicrobial therapy was insufficiently targeted at known resistance patterns of likely or cultured pathogens, clearly leaving room for improvement.

Table 2
Antimicrobial coverage of *in-vitro* cultured pathogens (41 patients)

Drug choice	Pathogens covered N patients (% covered)	95% CI
Ciprofloxacin	27 (66%)	(49%–80%)
Guideline drugs	32 (78%)	(62%–89%)

Reliability of reported ingestion in paracetamol overdose

J. Mulder[1], C. Meulendijks[2], C. Neef[3], S. Natsch[4] & C. Kramers[1]
[1]Department of Pharmacology/Toxicology, [2]MTA and [3]Department of Pharmacy, Medisch Spectrum Twente, Enschede, and [4]Clinical Pharmacy, UMC 'Nijmegen', P.O. Box 9101, 6500 HB Nijmegen

Introduction: The reported ingestion of patients presenting with a paracetamol overdose may be unreliable. In the literature ingestion of less than 150 mg/kg is reported to be safe. If this presumption is correct, patients reporting a ingestion of less the 150 mg/kg can be sent home and no paracetamol level has to be measured. At present it is unknown what patient characteristics predict reliability.

Aim of the study: 1) To compare the reported amount of paracetamol ingestion to the paracetamol level in the Rumack nomogram, and determine whether reported ingestion of less than 150 mg/kg predicts a safe paracetamol level. 2) To identify denominators of unreliabilty by correlating the calculated reliability with patient characteristics.

Materials and Methods: Based on paracetamol levels measured between 1990 and 2000 in a university hospital and a large teaching hospital 260 intoxications were identified. Fourteen cases were lost for follow up, so 246 intoxications in 197 patients were studied. Firstly, the reported ingestion was plotted against the blood level. Secondly, if two levels were available using the computer program MWPharm the ingested dose was estimated. In this procedure Kel (elimination rate constant) was calculated using the two available levels, all other population pharmacokinetic parameters were fixed and next the ingested dose was estimated 'by hand'. Next the 'reliability index' (= RI) was calculated by deviding the estimated amount by the reported ingestion. Unreliablity was defined as an RI >2 or <0.5.

RI was correlated with age, gender, co-intake of benzodiazepines or alcohol, first attempt and psychiatric history. Statistical analysis was performed using SPSS software. $P < 0.05$ was considered significant.

Results: In 59 intoxications the reported intake was less than 150 mg/kg. In three of them the level was above the treating line of the nomogram. In 63 intoxications two paracetamol levels were available. In 20 of them RI was >2 or <0.5. Higher age (>40 years) was the only factor significantly correlated with unreliability.

Conclusion: 1) Since reported ingestion of <150 mg/kg may result in a paracetamol level above the treatment line, also in these patients the level should be assessed. 2) Higher age predicts unreliability.

Amoxicillin pharmacokinetics in (pre)term neonates

S. Reijntjens[4], C. Guillaume[1], L. Stolk[1], P. L. J. Degraeuwe[2], F. H. M. Nieman[3] & A. De Boer[4]
[1]Dpts of Clinical Pharmacy, [2]Pediatrics and [3]Clinical Epidemiology, [4]University Hospital of Maastricht and Dpt of Pharmacoepidemiology and Pharmacotherapy, Faculty of Pharmaceutical Sciences, Utrecht, The Netherlands

Introduction: Combination therapy with amoxicillin and gentamicin is used in our hospital to treat early onset infection of neonates. In contrast with gentamicin, amoxicillin plasma concentrations are not measured routinely. Because very few data about plasma concentrations and pharmacokinetics of amoxicillin are available, we have done a pilot study.

Objectives: Determination of plasma concentrations and pharmacokinetics of amoxicillin and investigation of the correlation of clinical and demographic characteristics with kinetic parameters.

Methods: We have measured amoxicillin concentrations with HPLC in surplus plasma from routine assays. Data of 24 (pre)term neonates were analyzed. The amoxicillin dose was 100–200 mg/day in two doses (n = 23) and three doses (n = 1). Mean (± sd) Gestational Age (Ga), Post Natal age (PNA) and number of plasma levels were respectively 34.0 (4.9) weeks, 2.2 (1.7) days and 4.5 (1.4) levels/infant. Because literature indicates, that plasma creatinine (pcr) in the first weeks of life does not reflect glomerular filtration rate [1], data of concomitant gentamicin monitoring, 5.4 (1.5) levels/infant, were also collected. Pharmacokinetic parameters were calculated with MW/PHARM 3.50 kinetic software (Mediware, The Netherlands). Statistical analysis was done with SPSS 11.0 (Chicago, IL, USA).

Results: Dose, top and trough concentrations around second dose and pharmacokinetic parameters of amoxicillin are shown in the table below. Because of the wide range in GA, the total population was split into two subgroups. There was a significant ($p < 0.01$) difference for Kel but not for V/W between the two subgroups.

	N	Kel (1/h)	V/W (l/kg)	Top (mg/l)	Trough (mg/l)	Dose (mg/kg/d)
GA < 34	14	0.1398 (0.048)	0.580 (0.116)	127 (62)	23 (13)	122 (40)
GA > 34	10	0.246 (0.060)	0.554 (0.130)	7 (5)	7 (5)	117 (34)

Significant Pearson's correlations were found between Kel_{amox} and GA, pcr, and Kel_{genta} ($p < 0.01$) and plasma urea concentration ($P < 0.05$). r was respectively 0.639, –0.564, 0.816 and –0.470. No correlation was found between V/W and other covariates.

Discussion and conclusions: For time-dependent antibiotics like amoxicillin, a $T_{>MIC} > 70\%$ or even a continuous target concentration of 4 × MIC have been proposed. In the light of our measured amoxicillin concentrations, we suggest to administer the actual daily dose in three gifts for neonates with GA > 34 weeks. Presently the number of included neonates is still too small for calculation of reliable predictive algorithms with multiple regression analysis. However the high Pearson's correlation suggests the possibility of dose correction with routinely measured gentamicin elimination rate.

1 Guignard JP, et al. Pediatrics 1999; 103: e49.

Prevalence and determinants of undertreatment of hypertension in the Netherlands

H. Schelleman[1,2], O. H. Klungel[2], W. M. M. Verschuren[3], A. De Boer[2], B. H. Ch. Stricker[1] & D. Kromhout[4]

[1]Department of Epidemiology & Biostatistics, Erasmus MC, Rotterdam, Netherlands, [2]Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht, Netherlands, [3]Centre for Prevention and Health Care Research, National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands, [4]Division of Nutrition and Consumer Safety, National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands

Background: Hypertension is a major risk factor for cardiovascular diseases. Therefore detection and adequate treatment of hypertension is important to reduce the incidence of cardiovascular diseases.

Objectives: To assess prevalence and determinants of undertreatment of hypertension in the general Dutch population.

Methods: We used data from a cross-sectional population based survey in Amsterdam (A), Maastricht (M), and Doetinchem (D) in the Netherlands. Between 1996 and 2001 12 762 men and women, aged 20–79 years, were screened for CVD risk factors. Hypertension was defined according to the Dutch guidelines of 1997: DBP 95 mm Hg and/or SBP 160 mm Hg, and/or the use of antihypertensive medication for the treatment of hypertension. Among treated patients uncontrolled hypertension was defined as DBP 90 mm Hg or SBP 160 mm Hg. Treatment eligibility was, according to recent guidelines, based on a multifactorial risk profile Multivariate logistic regression was used the assess determinants of undertreatment.

Results: Prevalence of hypertension among men (20–69 years) was 11.0% and for women (20–79 years) 15.6%. A total of 57% of the hypertensive men and 70% of the hypertensive women were receiving antihypertensive medication. Of those treated, 44% of the men and 33% of the women were controlled. Thirty three percent of the untreated hypertensive men and 41% of the untreated hypertensive women were eligible for treatment. Among treated hypertensives, use of cholesterol lowering drugs (OR; 0.41 [95% CI: 0.19–0.87]) was significantly associated with better blood pressure control. Increasing age (OR; 0.95 [95% CI: 0.92–0.99]), cholesterol medication (OR; 0.26 [95% CI: 0.13–0.53]), and diabetes (OR; 0.15 [95% CI: 0.03–0.70]) were factors associated with a higher probability of receiving treatment.

Conclusions: More than one third of the untreated hypertensives are eligible for treatment, whereas more than half of the treated hypertensives have uncontrolled blood pressure. We also identified several risk factors for undertreatment of hypertension, which allows to identify and approach groups of patients that need extra attention for their hypertension treatment.

Thiazide diuretics and the risk of hip fracture

M. W. C. J. Schoofs[1,2], M. van Der Klift[1,2], A. Hofman[1], C. E. D. H. De Laet[2,3], R. M. C. Herings[4], H. A. P. Pols[2] & B. H. Ch. Stricker[1,2,5]

[1]Pharmaco-epidemiology Unit, Department of Epidemiology & Biostatistics, Erasmus MC, Rotterdam, the Netherlands, [2]Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, [3]Department of Public Health, Erasmus MC, Rotterdam, the Netherlands, [4]PHARMO Institute, Utrecht, the Netherlands, [5]Drug Safety Unit, Inspectorate for Health Care, The Hague, the Netherlands

Introduction: Since the majority of hip fractures are related to osteoporosis, treatment of accelerated bone loss can be an important strategy to avoid occurrence of hip fractures. Thiazides have been associated with reduced age-related bone loss by decreasing urinary calcium excretion.

Aims: To examine the association between dose and duration of use of thiazide diuretics and the risk of hip fracture, and to study the consequences of discontinuation.

Methods: We used data from the Rotterdam Study, a prospective population-based cohort study in 7983 people aged 55 years and over. All hip fractures in the study period between June 1, 1991 and December 31, 1999 were reported by the general practitioners and verified by trained research assistants. Information on potential risk factors was gathered during an interview and clinical examination at baseline. Details of all dispensed drugs were available on a

day-to-day basis. To study the association between duration of thiazide use and hip fracture, exposure was divided into 7 mutually exclusive categories: no use, current use for 1–42 days, current use for 1–365 days, current use for >365 days, last use since 1–60 days, last use since 61–120 days and last use since >120 days. A Cox proportional hazard model with time-varying exposure was used to determine the risk of incident hip fracture with thiazide use.

Results: During an average follow-up of 7.4 years, 281 cases of hip fracture occurred. Relative to non-use, current use of thiazides for >365 days significantly reduced the risk of hip fracture (hazard ratio: 0.39 [95% CI: 0.18–0.85]). There was no clear dose-dependency. The protective effect gradually disappeared during a period of 4 months after discontinuation of thiazide use.

Conclusion: This prospective study demonstrates that thiazide diuretics protect against hip fracture but that this protective effect disappears within months after discontinuation.

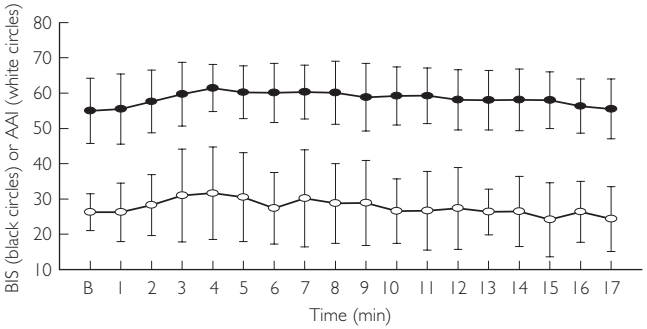
Electro-encephalographic surrogate measures fail to describe the pharmacodynamic interaction between ketamine and propofol

M. M. R. F. Struys, H. E. M. Vereecke & E. P. Mortier

Dept. of Anesthesia, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium

Aim of the study: Ketamine potentiates the effects of propofol on hypnotic signs like 'unresponsiveness to verbal command' and 'loss of eyelash reflex' (1). Bispectral index (BIS), an electro-encephalographic (EEG) derived index, and AAI (A-Line ARX-Index), a mid-latency auditory evoked potential (MLAEP) derived index, measure the pharmacodynamic effect of hypnotic drugs (2). As the clinical signs of the hypnotic state with propofol appear potentiated by ketamine, one might expect a reduction in BIS and AAI values. The present study investigates the accuracy of both BIS and AAI as surrogate measures of the pharmacodynamic interaction between ketamine and propofol.

Methods: After IRB approval and written Informed Consent, 15 otherwise healthy patients, scheduled for orthopedic surgery, were included. BIS and AAI were monitored with frontal electrodes using BIS-XP EEG (Aspect ®, Newton, Il, USA) and A-Line AEP (Danmeter, Odense, Denmark). First, loss of consciousness (LOC) was induced by infusion of propofol at 100 ml/h until loss of eyelash reflex and lack of response to verbal command. The calculated propofol effect-site concentration (Ce prop) at LOC was maintained by means of a PK/PD driven computerized infusion. A steady state Ce prop was reached at 4 min after LOC. Then, baseline BIS and AAI were measured for 1 minute. Five minutes after LOC a bolus ketamine (0.4 mg) was administered followed by an infusion of 1 mg/kg/h for 17 minutes. Baseline BIS and AAI were compared with all the minute by minute data, using a paired T-test with Bonferroni correction. Coefficient of variation (CV = standard deviation/mean) was calculated.



Results: Patients were 40 ± 16 years, 172 ± 8 cm, 67 ± 16 kg. Fig. 1 shows BIS and AAI changes from baseline (B) with ketamine. BIS increased ($p < 0.003$) from minute 3 to 8 after ketamine bolus without increase in CV. AAI didn't change with ketamine, but variability (described as CV) increased.

Conclusions: The expected decrease in BIS and AAI was not observed when combining propofol and ketamine. This makes them inadequate for measuring pharmacodynamic interaction. BIS changes can be explained by dominant frontal rhythmic theta activity with increased amplitude and AAI changes by a fluctuation in the primary sensory cortex or at a lower level.

1 Acta Anaesth Sc 1999; 43: 212.
2 Anesthesiology 2002; 96: 803.

Bioavailability of ibuprofen from hot-melt extruded mini-matrices

W. M. van Den Abeele[1], C. De Brabander[2], C. Vervaet[2], J. P. Remon[2] & L. M. van Bortel[1]

[1]Heymans Institute of Pharmacology, Ghent University, De Pintelaan 185, 9000 Gent, Belgium; [2]Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Gent, Belgium

Ibuprofen is a non-steroidal anti-inflammatory drug with a short half-life of approximately 2 hours. As a consequence, multiple daily dosing is required. Use of sustained release dosage forms can resolve this problem, enhancing patient compliance. The present study investigates the in-vivo performance of two novel mini-matrix formulations with sustained release properties in healthy volunteers, compared with a commercially available sustained release formulation as reference.

Methods: Each drug formulations contained 300 mg ibuprofen. The formulations tested were:

Data are presented as mean ± SD

	Ibu-slow®	F-1	F-2
T_{max} (h)	2.7 ± 0.8	4.1 ± 0.9	6.4 ± 3.8
C_{max} (μg/ml)	14.1 ± 3.4	7.8 ± 2.7[a]	6.1 ± 1.1[a]
$AUC_{0-24\ h}$ (μg.h/ml)	104.1 ± 34.0	79.0 ± 24.5[a]	80.9 ± 24.1[a]
$HVD_{t50\%Cmax}$ (h)	5.2 ± 2.0	7.6 ± 3.3	12.0 ± 6.3[a]

[a]$p < 0.05$ difference from Ibu-slow® according to a two-way ANOVA.

F-1: 30% ibuprofen, 35% ethylcellulose and 35% hydroxypropylmethylcellulose (Metolose® 60 SH 50),

F-2: 60% ibuprofen, 20% ethylcellulose and 20% xanthan gum

F-3: Ibu-slow® 600 mg (Therabel Brussels, Belgium, half a tablet).

Oral bioavailability was studied in a 3-period double blind randomised cross-over study. Nine apparently healthy subjects (3 males, 6 females) entered the study. They were from 18 to 55 years old, their weight and body mass index were within normal range. Formulations were given in fasting conditions. Washout between drug administrations was at least 6 days. Ibuprofen was assayed by HPLC-UV detection. Statistical analysis was done using a two-way analysis of variance (ANOVA) and Scheffe test.

Results: Of oral bioavailability are shown in Table 1.

$HVD_{t50\%Cmax}$: time period with plasma concentrations above 50% of C_{max}.

Conclusions: The present study shows that the mini-matrix formulated with hydroxypropylmethylcellulose (F1) and the mini-matrix formulated with ethylcellulose in combination with xanthan gum (F2) can be used as sustained release formulations. Especially the sustained release effect of the formulation with xanthan was statistically larger than the effect of the commercially available Ibu-slow®, as evidenced by the longer $HVD_{t50\%Cmax}$.

Human adenosine kinetics measured by microdialysis

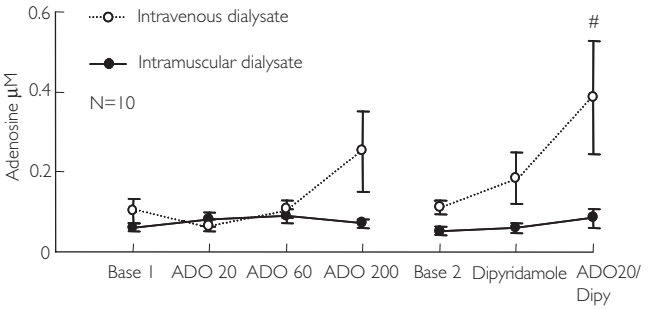
E. E. M. van Ginneken, Md[1], P. van Den Broek[2], P. Smits, Md, Phd[1,2] & G. A. Rongen, Md, Phd[1,2]

[1]Department of General Internal Medicine and [2]Department of Pharmacology-Toxicology, University Medical Centre Nijmegen, Nijmegen, The Netherlands

Background: Costa *et al.* (2000) described the microdialysis method as a promising tool to study human adenosine (ADO) kinetics at rest as well as during exercise. In protocol 1, we aimed to explore the contribution of catheter related tissue injury in exercise-induced ADO release. Protocol 2 explored whether the microdialysis technique is able to detect a gradient between circulating and interstitial ADO (as reported from in vitro studies), and to study the influence of the nucleoside transport inhibitor *dipyridamole* on the gradient between circulating and interstitial ADO.

Methods: Protocol 1: A microdialysis catheter was inserted into the flexor digitorum superficialis muscle. HPLC-measurement of intramuscular (IM) ADO, creatine (C) and creatine phosphate (CP) were performed during 2 bouts of intermittent handgrip, one hour apart, at 50% Fmax, for 15 minutes, every 5 seconds (n = 6 healthy volunteers). C and CP were measured as markers of myocytic cell damage (n = 4). Protocol 2: a second microdialysis catheter was inserted retrogradely into a deep cubital vene and the ipsilateral brachial artery was cannulated. Simultaneous measurements of IM and intravenous (IV) forearm ADO were performed during intrabrachial infusion of increasing ADO doses with/without dipyridamole (n = 10, see figure 1 for doses). Forearm blood flow (FBF) was measured by venous occlusion plethysmography.

Results: Protocol 1: 2 bouts of handgrip induced a rise in dialysate-ADO of 0.4 ± 0.2 vs 0.2 ± 0.1 nmol/ml (t-test n = 6, p > 0.1), and a rise in (C + CP) from 165 ± 7 vs 36 ± 22 nmol/ml (Wilcoxon, n = 4, p > 0.1). Protocol 2: Fig. 1 shows dialysate ADO concentrations during intra-arterial infusion of respectively saline, ADO 20, 60 and 200 nmol/min/dl of forearm volume, dipyridamole 200 nmol/dl/min and dipyridamole simultaneously with the lowest ADO dose:



During infusion of the lowest ADO dose with and without dipyridamole resp. FBF mounted 6.9 ± 1 vs 31.9 ± 3.9 (n = 10, p < 0.05), IM dialysate ADO concentrations were 0.08 ± 0.02 vs 0.06 ± 0.01 (n = 10, p = NS), and IV ADO concentrations were 0.07 ± 0.02 vs 0.2 ± 0.06 (p = 0.046).

Conclusions: The exercise-induced increase in interstitial adenosine is largely caused by catheter and exercise-related cell injury. Nucleoside transport prevents systemic spill of Adenosine during intra-arterial infusion. The microdialysis technique is able to detect the considerable gradient between intra-muscular and intravascular adenosine which is not relevantly reduced by dipyridamole.

Correlation between riluzole clearance and CYP1A2 activity in patients with amyotrophic lateral sclerosis

H. J. M. van Kan[1], G. J. Groeneveld[2], J. Sastre Toraño[1], M. Spieksma[1], L. H. van Den Berg[2] & H. J. Guchelaar[1]

[1]Academic Medical Center, Dept. of Clinical Pharmacy, P.O. Box 22660, 1100 DD Amsterdam, Netherlands, [2]University Medical Center Utrecht, Neuromuscular Center

Aims: Riluzole (Rilutek®) is the only drug licensed for the treatment of amyotrophic lateral sclerosis (ALS) and is prescribed in a fixed dosing schedule of 50 mg twice daily. Its pharmacokinetics (PK) in ALS patients is leading to variable serum drug concentrations.[1] Riluzole is assumed to be mainly metabolized by cytochrome P450 enzyme subtype 1A2 (CYP1A2). Variability in the enzyme activity may explain the drugs PK. A strong correlation of its clearance with CYP1A2 activity was expected. Results of this study may be useful to improve therapeutic outcome and to minimalize side effects.

Methods: Data were collected from 30 ALS patients from the outpatient clinic as part of a study protocol after approval by the hospital medical ethics committee. To estimate CYP1A2 activity the paraxanthine/caffeine molar serum concentration ratio was measured 6 hours after the administration of a 200 mg oral caffeine dose.[2] Individual riluzole clearance was estimated using peak and trough serum concentration measurements during steady state therapy with riluzole 50 mg bid and a Bayesian iterative procedure (1-compartment open model).[3,4] Riluzole, caffeine and paraxanthine serum concentrations were measured using validated liquid chromatographic assays.

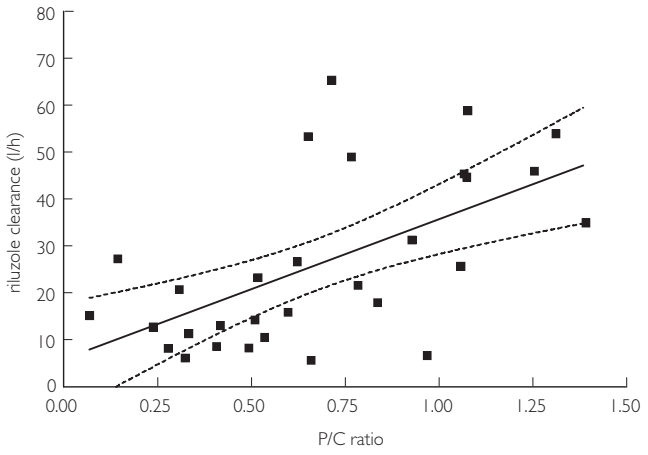


Figure 1
P/C ratio vs. riluzole clearance (n = 30)

Results: Between the P/C ratio and riluzole clearance we found a positive correlation (r = 0.594; p = 0.0005). See figure 1.

Discussion: Based on the correlation found in this study measurement of CYP1A2 activity offers a relatively simple method to roughly estimate the riluzole clearance in ALS patients. This may facilitate therapeutic drug monitoring and individualization of treatment. However, the correlation shows substantial residual variation that may be caused by other unknown factors. Also, a concentration-effect relationship has not been established.

Conclusions: This study shows a linear correlation between CYP 1A2 activity and riluzole clearance in patients with ALS.

1 J Neurol Sci 2001; 191(1–2): 121–5.
2 Biomed Chrom 1999; 13: 309–14.
3 Clin Pharmacol Ther 1997; 62(5): 518–26.
4 Lancet 1996; 348(9030): 795–9.

Calcitonin gene-related peptide-induced vasodilation in the human forearm: inhibition by the CGRP-receptor antagonist $CGRP_{8–37}$

F. H. M. Vanmolkot & J. N. J. M. De Hoon
Center for Clinical Pharmacology, University Hospital Gasthuisberg (K.U. Leuven), Leuven, Belgium

Calcitonin-gene related peptide (CGRP) is a potent endogenous vasodilator, for which at least two CGRP-receptor subtypes ($CGRP_1$ and $CGRP_2$) have been proposed. The C-terminal fragment of CGRP, $CGRP_{8–37,}$ is considered a moderately selective antagonist for the $CGRP_1$ receptor. *In vitro* and animal studies have shown that CGRP-induced vasodilation is inhibited by $CGRP_{8–37}$. However, human *in vivo* data confirming these results are still lacking.

The objectives of this study were to investigate the effects of $CGRP_{8–37}$ on resting forearm blood flow (FBF) and on CGRP-induced vasodilation *in vivo* in humans.

Bilateral venous occlusion plethysmography was used to assess FBF response to increasing infusion rates of CGRP (1, 3 and 10 $ng.min^{-1}.dL^{-1}$ forearm) into the brachial artery of 12 healthy subjects. Dose-response curves were constructed during co-infusion of CGRP and placebo (NaCl 0.9%). After washout (90 min), CGRP infusions were repeated during simultaneous infusion with placebo (time-control experiments, n = 6) and $CGRP_{8–37}$ (333 $ng.min^{-1}.dL^{-1}$ forearm, n = 6). FBF-ratio was calculated (FBF-ratio = FBF infused/FBF non-infused arm). Dose-response curves were compared using repeated measures ANOVA and Wilcoxon's matched-pairs signed-rank test. Data are presented as mean ± SEM.

FBF in the non-infused arm, blood pressure and heart rate did not change during the experiments. CGRP increased FBF from 3.2 ± 0.3 at baseline to 4.8 ± 0.3, 7.7 ± 0.7 and 12.7 ± 1.0 $mL.min^{-1}.dL^{-1}$ forearm, respectively ($P < 0.001$, n = 12). FBF-ratio during the first co-infusion of CGRP and placebo (1.9 ± 0.2, 3.1 ± 0.3 and 5.2 ± 0.8) did not differ from FBF-ratio during the second co-infusion of CGRP and placebo (2.1 ± 0.1, 3.0 ± 0.1 and 4.7 ± 0.3). Baseline FBF was not affected by infusion of $CGRP_{8–37}$ (3.1 ± 0.3 versus 3.1 ± 0.3 $mL.min^{-1}.dL^{-1}$ forearm). $CGRP_{8–37}$ attenuated the CGRP-induced increase in FBF-ratio (2.2 ± 0.3, 3.3 ± 0.2 and 5.7 ± 0.4 during infusion with placebo versus 1.6 ± 0.1, 2.0 ± 0.3 and 3.5 ± 0.6 during infusion with $CGRP_{8–37}$, $P = 0.012$).

Intra-brachial infusion of CGRP results in a dose-dependent and repeatable forearm vasodilator response. In the human forearm, $CGRP_{8–37}$ has no effect on resting blood flow, but effectively inhibits CGRP-induced vasodilation, suggesting involvement of the $CGRP_1$ receptor.

The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon

L. E. Visser[1,2], M. van Vliet[3], R. H. N. van Schaik[3], A. A. H. Kasbergen[4], P. A. G. M. De Smet[5,6], A. G. Vulto[2], A. Hofman[1], C. M. Van Duijn[1] & B. H. Ch. Stricker[1,7]

[1]Pharmacoepidemiology Unit, Departments of Internal Medicine and Epidemiology & Biostatistics, Erasmus MC, Rotterdam, the Netherlands, [2]Hospital Pharmacy, Erasmus MC, Rotterdam, the Netherlands, [3]Department of Clinical Chemistry, Erasmus MC, Rotterdam, the Netherlands, [4]Stichting Trombosedienst & Artsenlaboratorium Rijnmond, Rotterdam, the Netherlands, [5]Scientific Institute Dutch Pharmacists, The Hague, the Netherlands, [6]Department of Clinical Pharmacy, University Medical Centre St Radboud, Nijmegen, the Netherlands, [7]Drug Safety Unit, Inspectorate for Health Care, The Hague, the Netherlands

Introduction: Cytochrome P4502C9 (CYP2C9) is the main enzyme implicated in coumarin metabolism. The variant alleles CYP2C9*2 and CYP2C9*3 are associated with increased sensitivity to warfarin (Aithal *et al*., 1999; Taube *et al*., 2000; Higashi *et al.*, 2002; Scordo *et al.*, 2002). An effect on acenocoumarol dose requirements, however, seems to be absent or not clinically relevant (Thijssen *et al*., 2000; Hermida *et al*., 2002; Tassies *et al*., 2002) and the consequences for the metabolism of phenprocoumon has not yet been established.

Aim: We investigated CYP2C9 polymorphisms in relation to stability of the anticoagulant level during the first six weeks of treatment and its effect on the maintenance dose in a cohort of 1124 patients treated with acenocoumarol or phenprocoumon.

Methods: Independent-samples t tests were used for comparing the mean number of INR assessments and the mean INR during the first six weeks of treatment and the differences in mean maintenance dose during the rest of the follow-up between carriers of variant alleles and the wild type genotype. Relative risks (RR) with 95% confidence intervals (CI) were calculated for comparing the proportion of patients with an INR ≥ 6.0 between variant and wild type genotypes. A multivariate linear regression model was used to assess the effect of allelic variants on the coumarin maintenance dose, while controlling for differences in cofactors.

Results: After a standard starting dose of acenocoumarol, there was a statistically significant difference in the first INR between patients with the variant genotypes and those with the wild type. Almost all acenocoumarol-treated patients with a variant genotype had a significantly higher mean INR and had a higher risk of an INR ≥ 6.0 during the first six weeks of treatment. A clear genetype-dose relationship was found for acenocoumarol-treated patients. For patients on phenprocoumon no significant differences were found between variant genotypes and the wild type genotype.

Conclusion: Individuals heterozygous for either CYP2C9*2 or CYP2C9*3, as well as those with two variant CYP2C9 alleles require a significantly lower dose of acenocoumarol than wild type patients. Phenprocoumon seems to be a clinically useful alternative in patients carrying the CYP2C9*2 and *3 alleles.

1 Aithal GP, et al. Lancet 1999; 353: 717–19.
2 Hermida J, et al. Blood 2002; 99: 4237–9.
3 Higashi MK, et al. JAMA 2002; 287: 1690–8.
4 Scordo MG, et al. Clin Pharmacol Ther 2002; 72: 702–10.
5 Tassies D, et al. Haematologica 2002; 87: 1185–91.
6 Taube J, et al. Blood 2000; 96: 1816–19.
7 Thijssen HH, et al. Pharmacogenetics 2000; 10: 757–60.

Determinants of elevations of lithium serum levels into the toxic range

I. Wilting[1,2], M. Moolenaar[1], K. L. L. Movig[1], Y. A. Hekster[3], J. R. B. J. Brouwers[4] & A. C. G. Egberts[1,2]

[1]Hospital Pharmacy Midden-Brabant, TweeSteden Hospital and St. Elisabeth Hospital, Tilburg, Netherlands, [2]Department of Pharmacoepidemiology and Therapeutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands, [3]Department of Clinical Pharmacy, University Medical Centre Nijmegen, Nijmegen, Netherlands and [4]Hospital Pharmacy, General Hospital Tjongerschans, Heerenveen, Netherlands

Background: Lithium salts are the major treatment option in patients with bipolar disorder. An important limitation of the therapeutic use of lithium is, the narrow therapeutic window [0.6–1.2 mmol/L]; small increases in lithium serum level can result in toxic concentrations and related serious adverse reactions. Concomitant medication (co-medication) is a highly suspected cause of toxic lithium serum levels (Harvey *et al*., 1994). However, the impact of such drug-drug interactions in daily clinical practice is unknown.

Objectives: To determine the impact of co-medication on the elevation of lithium serum levels into the toxic range; ≥1.3 mmol/L.

Methods: A retrospective case-control study was conducted among Dutch patients on lithium treatment. Cases were patients ≥18 years of age having a regularly measured lithium serum level of ≥1.3 mmol/L and an increase of at least 50% relative to the previous measurement. Suspected intentional intoxications were excluded. Controls were randomly selected from patients having a lithium serum level within the therapeutic window on the index date, that differed less than 50% from the previous measurement. Both cases and controls had at least two lithium serum levels within the therapeutic window prior to inclusion and had been on lithium treatment for at least three months. Patient serum concentrations were collected for: creatinin, TSH, potassium and sodium. From the patients medical record information on type of physician, lithium doses (on the index and the pre-index date) and selected co-medication (use of NSAIDs, diuretics, RAS inhibitors, thyreomimetics, corticosteroids and antibiotics) was gathered. Starters on selected co-medication were identified. Starting was defined as a first prescription within 30 days before the index date and no prescription for that medication in the 120 days before.

Results: Forty-seven cases and an equal number of controls were included. Twenty-one cases and ten controls used co-medication (OR 3.0 [CI: 1.2–7.4]). Four cases and no controls were starters, OR 9.8 [CI: 0.5–187.9]. Cases were more frequently women (74%) than controls (60%), OR 2.0 [CI: 0.8–4.8]. No association was found with age, type of physician or change in lithium doses and toxic lithium serum levels.

Conclusions: From these results we conclude that (starting of) co-medication is a determinant for elevations of lithium serum levels into the toxic range, in daily clinical practice. Further research is necessary to elucidate what (classes of) drugs are most important and in which patients such drug-drug interactions occur.

Harvey et al., Drugs Safety 1994; 10(6): 455–63.