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Effects of Intravenous Aspirin on Prostaglandin Synthesis and Kidney Function in Intensive Care Patients

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Abstract. The effects of intravenous acetylsalicylic acid (1.0 g bolus) on renal function and prostaglandin synthesis were evaluated in a prospective, controlled study in eight patients in an intensive care unit. Four of these patients had congestive heart failure. Administration of acetylsalicylic acid caused significant antidiuresis (–56%), antinatriuresis (–82%), renin suppression (–26%) and decreased GFR (–41%). All of these changes were completely reversible within 1–2 hours and tended to be more pronounced in the patients with congestive heart failure. Urinary excretion of prostaglandin E_2 was depressed profoundly (–93%) and did not return to more than 45% of control 6 h after the administration of acetylsalicylic acid.

We conclude that intravenous acetylsalicylic acid affects kidney function in a manner similar to other prostaglandin synthesis inhibitors. Its effects are, however, short-lived. The inhibition of urinary PGE_2 excretion outlasts GFR depression, antidiuresis, antinatriuresis and renin suppression by several hours.

Key words: Aspirin; Prostaglandin E_2; Intensive care; Kidney function; Congestive heart failure

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Introduction

It is well recognized that prostaglandin synthesis inhibitors (PGSI) may impair renal function, particularly when effective arterial blood volume (EABV) is reduced. Thus, deterioration of renal function induced by PGSI has been described in sodium depletion [1], liver cirrhosis [2,3], nephrotic syndrome [4] and congestive heart failure (CHF) [5]. It has been proposed that renal blood flow becomes dependent on vasodilatory prostaglandins produced in the kidney whenever effective arterial blood volume is reduced [6]. These vasodilatory prostaglandins are thought to counteract increased catecholamine- and angiotensin-mediated vasoconstriction. Substances which *reversibly* inhibit cyclo-oxygenase, but have a relatively long pharmacological half-life, such as indomethacin, have been used in most studies. A similar effect, however, has not conclusively been shown for acetylsalicylic acid (ASA), which *irreversibly* inactivates cyclo-oxygenase [7,8], but has a half-life of only 10–15 minutes [9]. Additionally, aspirin in an injectable form (lysine-ASA, Aspegic) has been frequently used as an analgesic and antipyretic drug in our intensive care unit (ICU). We therefore undertook a study to assess the effects of intravenous aspirin on kidney function in ICU patients with and without congestive heart failure.

Methods

Patients

All patients admitted to the medical ICU of the Kantonsspital Basel between 1 September 1982 and 31 December 1982 were evaluated for the following entry criteria: (1) age above 40 years, (2) creatinine clearance above 20 ml/min, (3) the presence of an urinary catheter that would probably not be removed for the next 2 days, (4) no use of PGSI in the past 24 h, (5) no bleeding tendency and (6) no history of salicylate allergy. Only patients who fulfilled all these criteria were entered. Eight patients qualified for entry, all of whom completed the study (six men and two women; mean age 68; range 50–85 years). Admitting diagnoses included hypoxic brain damage after cardiac arrest due to myocardial infarction (three patients), congestive heart failure due either to chronic coronary heart disease (two patients) or to recent myocardial infarction (one patient), Pickwickian syndrome (one patient) and Guillain–Barré syndrome with tetraplegia (one patient). Presence or absence of congestive heart failure was determined prospectively in all eight patients. CHF was diagnosed, if two or more of the following criteria were present: (1) pulmonary capillary wedge pressure (PCWP) or pulmonary artery diastolic pressure (PAd) above 15 mmHg (measured without PEEP), (2) jugular vein distension or central venous pressure (CVP) above 12 mmHg, (3) pulmonary venous congestion on chest-x-ray, (4) basal pulmonary rales. There were four patients with and four without CHF.

Informed oral consent was obtained either from the patients, or from relatives if the patient was unable to communicate. The study was approved by the Ethical Committee of the University Hospital of Basel.

Protocol

Studies were performed on two consecutive days for every patient. Aspirin 1.0 g was given intravenously on one day while on the other day only a blood sample was drawn at the corresponding time. The sequence for each patient ('aspirin day'—'control day' or vice versa) was established separately within the 'non-CHF' and 'CHF' groups using a random sequence.

Before measurements, a thin plastic tube (Bard-I-Cath, normally used for peripheral vein cannulation) was introduced into the urinary catheter and advanced to its tip for air washout of bladder and catheter between urinary collections. The protocol was started between 8.00 and 10.00 a.m. with an intravenous loading dose of 0.5 ml 10% inulin (Inutest, Laevosan-Gesellschaft, Linz, Austria) followed by a continuous i.v. infusion of 5% glucose plus inulin. The inulin concentration in the infusion was calculated individually to yield an infusion rate of 0.25 mg/min × estimated GFR in an infused volume of 90–100 ml/h. At least 75 min were allowed for equilibration. Urine was then collected at 60-minute intervals for a total of 8 h. For prostaglandin determination, urine was collected in glass containers previously washed in methanol; samples were immediately frozen at −17°C. Urine samples with macroscopic haematuria were excluded from this determination. Blood samples were drawn at 1-h intervals for serum inulin, and at 2-h intervals for serum creatinine determination. Aspirin 1.0 g in a soluble preparation (lysine-ASA, Aspegic) was injected after two control urine collection periods, and measurements were continued for the subsequent 6 h. Plasma renin activity (PRA), noradrenaline and adrenaline were determined immediately before ASA, 1 h and 4 h after ASA, and at the corresponding times on the control day. Plasma salicylate levels were determined 1 h and 4 h after injection.

The treating physicians were not informed about the study phase in each individual patient (ASA day or control day). However, the investigation was not formally designed as a double-blind study. No prostaglandin synthesis inhibitors were allowed during the study, but with this exception the physicians in charge were not restricted in their therapeutic measures. Patients on diuretics or vasodilators were continued on their previous therapeutic schedule. Intravenous fluids were administered at a constant rate. Fluid and diuretic therapy was not changed during the 8 study hours.

Determinations

Serum and urine inulin was determined enzymatically [10]. Serum and urine electrolytes and creatinine were measured by a Technicon auto-analyzer. PGE_2 in urine was determined by radioimmunoassay (RIA) following extraction and purification by thin-layer chromatography. This method has previously been described and shown to yield results in agreement with mass spectrometric determinations [11]. Plasma renin activity (PRA) was determined as described [12]. Adrenaline and noradrenaline were determined by RIA [13]. Salicylate levels were determined by the Trinder method [14].

Statistical evaluation

Urinary prostaglandin determination was not carried out in patient No. 2 because of macrohaematuria. Patient 6, in the second hour after ASA, was so oliguric that prostaglandins could not be assayed. With these exceptions, data collection was complete.

Data were analysed separately for the ASA and control days by 2-way analysis of variance, using time and individual patients as influencing factors. Logarithmic transformation was used for all parameters except the $C_{inulin}/C_{creatinine}$ ratio. All 'mean values' in this paper therefore represent

mean values of the decimal logarithms of the original parameters, which were transformed back to the original scale by 10^x for better comparison. Although not used in the calculations, standard errors of the log-means are indicated, to enable evaluation of the variability between patients. A parameter was considered significantly different from baseline if the analysis of variance yielded a significant F-test for treatments ($P<0.05$) and if, in addition, the value was found to be significantly different from each of the two control measurements using Duncan's new multiple range test with $P<0.05$ [15,16].

Results

Inulin clearance (Fig. 1) decreased significantly from 65 ml/min to 38 ml/min in the first hour after ASA. The decrease in inulin clearance was also significant in the four patients with CHF (decrease from 51 ml/min to 26 ml/min in the second hour after ASA). The smaller decrease in the patients without CHF (83 ml/min to 50 ml/min) was not significant. No change was observed on the control day.

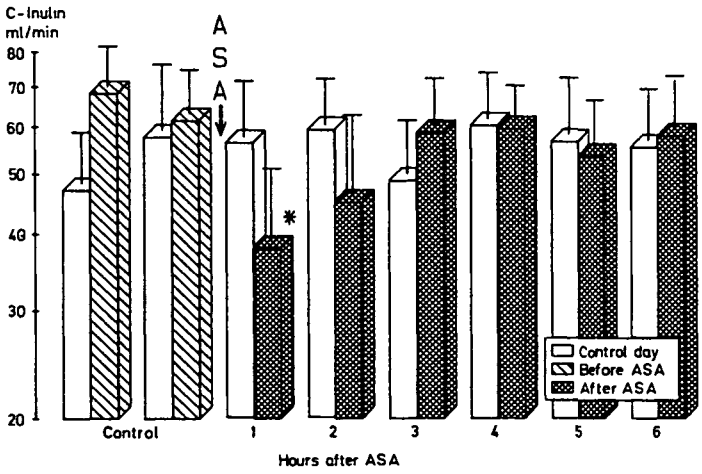

Fig. 1. Inulin clearances of the eight patients on control (white bars) and ASA days (hatched bars). The ANOVA for the ASA day was significant for an effect of treatment ($P<0.005$). *denotes significant difference from both control values pre-ASA in Duncan's test ($P<0.05$). Data are presented as log means and log SEMs.

Creatinine clearance paralleled inulin clearance. There was no significant change in the $C_{inulin}/C_{creatinine}$ ratio on both ASA and control days (Table 1).

Urine volume (Table 1) decreased significantly from 104 ml/min to 46 ml/min in the second hour after ASA. As with inulin clearance, changes tended to be more pronounced in the CHF subgroup (decrease from 117 to 31 ml/min 2 h after ASA, $P<0.05$) than in the subgroup without CHF (decrease from 93 to 58 ml/min; not significant). No change was seen on the control day.

Urinary sodium excretion (UNaV, Table 1) decreased significantly from 49 μEq/min to 9 μEq/min in the second hour after ASA. The changes in the two subgroups were not significant, due to considerable variation both between and within patients. No change was observed on the control day.

ASA significantly decreased *urinary PGE_2 excretion* ($UPGE_2V$, Fig. 2) from 27 ng/h to a minimum of 2 ng/h during the second hour after ASA. Even 6 h after ASA, PGE_2 excretion had not returned to more than 12 ng/h. However, in the four patients given ASA on day 1 and in whom PGE_2 determination was repeated after 24 h, PGE_2 excretion had completely recovered. There was no significant change on the control day. Baseline values showed no clear-cut difference between CHF and non-CHF patients, in fact the two highest rates and the lowest rate were found in the CHF group.

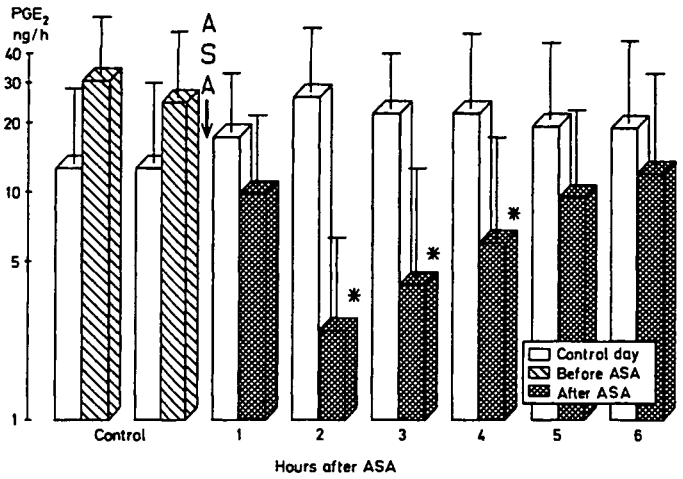

Fig. 2. Urinary PGE_2 excretion of seven patients on control (white bars) and ASA days (hatched bars). The ANOVA for the ASA day was significant for an effect of treatment ($P<0.001$). *denotes significant difference from both control values pre-ASA in Duncan's test ($P<0.05$). Data are presented as log means and log SEMs.

Plasma renin activity was higher on average in the CHF compared to the non-CHF group. When both groups were analysed together, there was a significant decrease at 1 h after ASA from 23 ng AI/ml per h to 17 ng AI/ml per h (Table 1). No significant change was observed on the control day.

Plasma adrenaline and *plasma noradrenaline* levels were very high in all patients. Pre-ASA values were 231 ± 1.3 ng/ml for adrenaline (normal 15–80 ng/ml) and 1335 ± 1.2 ng/ml for noradrenaline (normal: 140–700 ng/ml). No significant change was found.

Serum salicylate levels decreased from a mean of 0.49 nmol/l (range 0.36–0.57 nmol/l) 1 h after ASA to 0.36 nmol/l (range 0.27–0.48 nmol/l) 4 h after ASA. There was no difference between CHF and non-CHF patients.

Discussion

The most prominent effects of ASA in this study were GFR depression, antidiuresis, antinatriuresis, and renin sup-

Table 1. Urine volume, urinary sodium excretion, plasma renin activity and $C_{inulin}/C_{creatinine}$ ratio

	Day	Before	ASA	Hours after ASA						*P* value[a]
				1	2	3	4	5	6	
Urine volume (ml/h)	Control	71	65	71	99	81	102	121	103	n.s.
	±SEM	1.3	1.3	1.3	1.4	1.4	1.3	1.4	1.3	
	ASA	93	117	54	46[b]	86	100	103	95	$P<0.01$
	±SEM	1.3	1.3	1.1	1.4	1.4	1.3	1.3	1.4	
$U_{Na}V$ (μeq/min)	Control	43	31	36	46	26	63	73	58	n.s.
	±SEM	1.9	2.0	1.8	1.7	2.1	1.9	1.6	1.8	
	ASA	40	61	23	9[b]	19	32	42	37	$P<0.05$
	±SEM	1.8	1.5	1.5	1.7	1.6	1.6	1.5	1.7	
Plasma renin activity (ng AI/ml/h)	Control		17	18			17			n.s.
	±SEM		1.8	1.6			1.7			
	ASA		23	17[b]			20			$P<0.05$
	±SEM		1.4	1.4			1.4			
$C_{inulin}/C_{creatinine}$	Control	0.98	1.06	1.08	1.01	1.02	1.00	1.02	0.96	n.s.
	±SEM	0.04	0.06	0.04	0.06	0.03	0.03	0.07	0.05	
	ASA	1.07	1.02	1.03	1.07	1.00	0.98	0.92	1.06	n.s.
	±SEM	0.07	0.07	0.09	0.06	0.07	0.05	0.08	0.07	

All numbers are the mean values (n = 8) of the logarithms transformed back to the original scale; to obtain the ± 1 SEM interval, multiply or divide the means by the SEMs. The $C_{inulin}/C_{creatinine}$ values are arithmetic means ± SEM.

[a] *P* value of the F-Test for treatments (observation periods) in the 2-way ANOVA. A significant *P* value indicates that the differences between observation periods exceed the random variation.

[b] denotes significant difference from both control values of the same day in Duncan's test.

pression, which are well-known renal effects of prostaglandin synthesis inhibitors. Up to now, however, no study has reported the full spectrum of PGSI effects after ASA. For example, renin suppression was never found [1,17], and in one study the absent antidiuretic or antinatriuretic effects of ASA were contrasted with the pronounced effects of indomethacin [18].

Based on current knowledge, it is plausible that prostaglandin (PG) inhibition should cause the effects observed. GFR depression is usually attributed to unopposed preglomerular vasoconstriction [6]. As prostaglandins are known to antagonize the hydro-osmotic effects of antidiuretic hormone (ADH) on the distal nephron [19,20], PGSI-induced antidiuresis is explained by enhanced ADH action in the absence of prostaglandins. Mechanisms considered for PGSI-induced antinatriuresis include: (a) renal vasoconstriction by lack of vasodilatory prostaglandins [21,22,23], (b) more avid distal tubular sodium reabsorption which would normally be inhibited by prostaglandins [23], and (c) direct aldosterone-like effects of PGSIs, particularly ASA [17]. Finally, renin release is stimulated by prostacyclin (PGI_2) [24,25,26], and, accordingly, renin suppression has frequently been described after indomethacin [21,27,28,29].

It is of interest that in our study, all of these effects were much shorter in duration (2 h) than the effect on PGE_2 excretion, which, 6 h after ASA, was still 50% below baseline. PGE_2 in urine originates from the kidney [30], and reflects essentially medullary cyclo-oxygenase activity [24,31]. As ASA acetylates cyclo-oxygenase irreversibly [7,8], and as its metabolite salicylic acid does not inhibit prostaglandin synthesis in oral doses up to 1.2 g t.i.d. [32], it can be inferred that the gradual recovery of PGE_2 excretion in our study reflects resynthesis of medullary cyclo-oxygenase.

Several explanations for this incongruence in the time course of PGSI-effects and PG synthesis inhibition are conceivable: GFR depression and renin suppression could revert earlier, because resynthesis of cyclo-oxygenase in the renal cortex might be more rapid than in the medulla; furthermore, only relatively little cyclo-oxygenase activity might be needed to counteract vasoconstriction. The rapid reversal of antidiuresis could indicate that medullary PGE_2 synthesis is not relevant to the effects of ADH on the distal nephron, or that overriding regulatory mechanisms came into play to restore urine output. Similar explanations apply to antinatriuresis.

In comparing our data with earlier studies on ASA, one notes that GFR effects of similar magnitude were observed only by Berg [22], who administered 750 mg of ASA intravenously to patients with chronic renal failure, which caused GFR to decrease by 40%. Some of the lupus patients studied by Kimberly and Plotz [33] under therapy with oral ASA also experienced large reductions in GFR. Using 1.0 g of intravenous ASA, Robert et al. [34] studied eight patients recovering from minor illness, and found an average reduction in C_{inulin} of 30%. The remaining studies found little or no effect on GFR [1,17,35,36]. All of them used oral ASA. We could

not confirm the finding of Burry and Dieppe [35] that ASA caused a decrease in creatinine clearance (not GFR) due to inhibition of tubular creatinine secretion. The following factors might have contributed to the magnitude of GFR reduction in our study:

(1) *Oral vs. iv. ASA.* Given the low bioavailability of ASA after oral ingestion (approximately 50% with single ASA doses of up to 1300 mg, [9]), it is conceivable that i.v. ASA inhibits PG synthesis much more effectively than oral ASA. Although Vierhapper et al. [18] found similar (70–75%) inhibition of $UPGE_2V$ with 3 g/day of oral ASA and with indomethacin 150 mg/day, this does not rule out differences in renal cortical PG synthesis inhibition.

(2) *Reduced effective arterial blood volume (EABV).* EABV was certainly reduced in the patients with CHF, as evidenced by their low baseline GFR. After ASA, GFR seemed to decrease to a greater extent in these patients, but the difference between the CHF and non-CHF groups was not significant, and even without CHF or clinical evidence of reduced EABV, two patients had large reductions in GFR of 48% and 71%.

(3) *Vasoconstrictors.* Our patients had high levels of adrenaline, noradrenaline and renin. Noradrenaline, and under certain conditions angiotensin II, are potent stimulators of renal PG synthesis in vivo [37] and in vitro [38,39]. Although catecholamine levels did not correlate with the magnitude of GFR depression, the two non-CHF patients who experienced the least decrease in GFR (–3% and –9%) also had the lowest (almost normal) plasma adrenaline and noradrenaline levels of all the study patients.

In summary, we conclude that intravenous ASA affects kidney function in a manner similar to other PGSIs. Its effects are, however, short-lived. Medullary PG synthesis inhibition outlasts GFR depression, antidiuresis, antinatriuresis and renin suppression by several hours.

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