Pharmacokinetics of the thromboxane A₂ receptor antagonist sulotroban (BM 13.177) in renal failure

C. PIPER, Ch. STAIGER, Y. JUMEAU-ZIEMENDORFF, V. UEBIS, B. KAUFMANN & K. STEIN
Medizinische Klinik A, Klinikum der Landeshauptstadt Wiesbaden, (Chief Consultant: Prof. Dr H. V. Egidy)
and Clinical Research Department, Boehringer Mannheim GmbH, FRG

1 Ten healthy volunteers and 26 hospital in-patients with endogenous creatinine clearances of 98 to 4 ml min⁻¹ received an oral dose of 800 mg sulotroban (BM 13.177). The plasma and urine concentrations of sulotroban were measured by gas-chromatography over 72 h and the pharmacokinetic parameters were calculated.

2 The AUC rose from 28.5 mg l⁻¹ h in healthy volunteers to 631.4 mg l⁻¹ h in preterminal renal failure (medians). The CL_R decreased from 317.0 ml min⁻¹ to 6.5 ml min⁻¹ at the lowest renal capacity.

3 According to the AUC values, reduction of the dose is not necessary at CL_{Cr} > 50 ml min⁻¹, a dose of 20–40% of normal is appropriate at CL_{Cr} of 20–50 ml min⁻¹. At CL_{Cr} ≤ 20 ml min⁻¹ the normal dose should be reduced to < 20% of normal.

4 Vaginal spotting was noted in three female patients and a gastro-intestinal haemorrhage that did not require transfusion in one male patient. These may be associated with the action of sulotroban.

Keywords pharmacokinetics renal failure thromboxane A₂ receptor antagonist sulotroban (BM 13.177) adverse effects

Introduction

Thromboxane A₂ (TXA₂) arises as a main metabolite of human arachidonic acid metabolism. TXA₂ induces platelet aggregation and vasoconstriction (Moncada & Vane, 1979). It plays an important role in septic shock (Wise *et al.*, 1981). During myocardial ischaemia, arrhythmias are mediated by TXA₂ (Coker & Parratt, 1985), and angina pectoris attacks in coronary artery disease can be induced by this compound (Mehta *et al.*, 1979). Hypoperfused kidneys release increased amounts of TXA₂ (Pretus & Feigen, 1986). Intrarenal synthesis is also increased in immunological rejection of renal transplants (Foegh *et al.*, 1982) and in lupus nephritis (Ciabatoni *et al.*, 1982). Intra-

renal vasoconstriction in unilateral hydronephrosis is mediated by massive TXA₂ release (Morrison *et al.*, 1981; Huland *et al.*, 1983).

Sulotroban (BM 13.177), 4-[2-[benzenesulphonamido)-ethyl]-phenoxyacetic acid has been described as a selective, specific and competitive TXA₂ receptor blocker (Stegmeier *et al.*, 1984). Sulotroban is active in humans on platelets and vessels (Gresele *et al.*, 1984). Its pharmacokinetics have been investigated in healthy volunteers. The important parameters were found to be a terminal elimination half-life of 0.85 h, a urinary recovery of 52% of the dose administered, a total clearance of 741 ml min⁻¹ and a renal clearance in the range of 310 to 396

ml min⁻¹. There was a close correlation between the plasma drug concentration-time profile and the action on platelets (Staiger *et al.*, 1986).

Pilot investigations in patients undergoing chronic haemodialysis indicated a marked delay in the elimination of sulotroban in end-stage renal failure (Pedrosa, personal communication). These results prompted the following study to investigate the pharmacokinetic parameters in relation to different degrees of renal function.

Results have been presented in part at II. World Conference on Clinical Pharmacology and Therapeutics, Stockholm, 1986 (*Acta Pharmac. Tox.* 1986, Suppl. 5, A 910) and 28th Spring Meeting of the German Society of Pharmacology and Toxicology, Mainz 1987 (*Naunyn-Schmiedeberg's Arch. Pharmac.* 1987, 335 Suppl., R 40). The paper consists essentially of parts of the dissertation by Y. Jumeau-Ziemendorff.

Methods

Healthy male volunteers and hospital in-patients of both sexes who had different degrees of stable restricted renal function were entered into the study.

Ten healthy volunteers, aged 19–37 years, were examined clinically before and after the study and underwent standard chemical and haematological tests (sodium, potassium, creatinine, cholesterol, triglycerides, blood sugar, glutamate oxalo acetate transpeptidase (GOT), γ -glutamyl transpeptidase, bilirubin, erythrocyte count, haemoglobin, leucocyte count, platelet count and urinalysis). None of the volunteers had taken any medication before the examination. They were non-smokers. The study was described to the volunteers and they gave their written consent after the local ethics committee had given its approval for this study.

Twenty-six patients of both sexes, aged 40 to 80 years who had stable restricted renal function of different degrees were enrolled in the study.

The concurrent medication during the study was recorded, but was not altered. The blood count, sodium, potassium, glutamate pyruvate transpeptidase (GPT), urea, total protein, creatinine, partial thromboplastin time and Quick value were determined before and after the investigation. Adverse events were also recorded. The study was explained to the patients and they gave their written consent in the presence of witnesses.

Criteria for exclusion of patients were: severe impairment of general well-being, taking drugs that act on arachidonic acid metabolism, taking

of β -lactam antibiotics, taking of antacids or histamine-H₂ receptor antagonists, haemorrhagic diathesis, impaired liver function (GPT > 50 u l⁻¹), ulcerative gastro-intestinal tract lesions and hypertension > 180/100 mm Hg resistant to therapy.

Volunteers and patients were admitted consecutively to the study until the following groups were obtained:

- Group I: Creatinine clearance 0–20 ml min⁻¹ (8 patients)
- Group II: Creatinine clearance 21–50 ml min⁻¹ (10 patients)
- Group III: Creatinine clearance 51–100 ml min⁻¹ (8 patients)
- Group IV: Creatinine clearance >100 ml min⁻¹ (10 volunteers)

For inclusion of the volunteers in the study, the creatinine clearance was calculated according to the equation of Cockcroft & Gault (1976) from plasma creatinine concentration, body weight, height and age. In the patients, the creatinine clearance was calculated from plasma creatinine concentration, amount of creatinine excreted and urine volumes according to the standard method. Patients and volunteers were given 800 mg sulotroban in tablet form (Batch No. 818 546 A) with 100 ml fluid in the morning on an empty stomach and breakfast was given 2 h later. Blood samples were collected from the patients after 0, 1, 2, 3, 4, 5, 6, 8, 12, 24, 30, 36, 48 and 72 h. Up to the 24th hour, additional samples were collected from the volunteers at 0.5, 1.5, 2.5, 3.5, 4.5, 5.5 and 7 h. Urine samples were collected from 0–4 h, 4–8 h, 8–12 h, 12–24 h in patients and volunteers alike. In the patients further samples were collected from 24 to 48 h and from 48 to 72 h after drug ingestion. Plasma and an aliquot of each urine sample were stored until analysis at –20°C.

Sulotroban concentrations in plasma and urine were measured by gas-chromatography (Staiger *et al.*, 1986). The assay limit for sulotroban was 100 ng ml⁻¹ in serum and 810 ng ml⁻¹ in urine, with a coefficient of variation of less than 10%. Standard pharmacokinetic parameters were calculated as shown in Table 2. The relationship between AUC and CL_{Cr} was evaluated by linear regression taking AUC as the dependent and the inverse CL_{Cr} as the independent variable. All of the data are given as medians with range. The calculation for adjustment of the dose was carried out according to the equation $AUC_g/AUC \times 100$, where AUC_g is the mean area after administration of sulotroban to healthy volunteers and AUC is the area after administration of sulotroban to the patients.

Results

The 10 male volunteers with creatinine clearances from 131 ml min^{-1} to 203 ml min^{-1} were enrolled in group IV. All of the volunteers completed the study.

The patients' clinical data are shown in Table 1. Groups I and III each comprised eight patients but group II (creatinine clearance $21\text{--}50 \text{ ml min}^{-1}$) comprised 10 patients instead of the planned eight. The data from patient no. 6 in this group were not evaluable as no sulotroban was detected in the urine and plasma. The patient later admitted that he had not taken the drug. The urine collection from 24 to 72 h was missed in patient 24. Therefore, only the plasma and urine drug concentrations up to 24 h after dosage were evaluated.

The pharmacokinetic data are listed in Table 2. The plasma drug concentration-time curve and cumulative excretion of sulotroban in urine are shown in Figures 1 and 2. The maximum plasma concentrations of sulotroban rose in relation to the degree of renal failure. In groups II–IV the t_{max} remained at 1.0–1.5 h, whereas in group I it increased to 3.5 h.

The AUC increased progressively from groups IV to group I in accordance with the deterioration in renal function.

The terminal elimination half-life of sulotroban was prolonged with increasing impairment of renal function reaching a value of 18.9 h in group I (Figure 1, Table 2).

The cumulative 24 h urinary recovery of sulotroban in groups II, III and IV was 60 to 63% of the oral dose and did not increase appreciably beyond this time. In group I, the median urinary recovery up to 72 h was 23.5% of the administered dose (Figure 2).

Figure 3 shows the dependence of the AUC on the creatinine clearance. Below a creatinine clearance of $25\text{--}30 \text{ ml min}^{-1}$ the AUC increased markedly.

Adverse events

Adverse events occurred during the study in three female patients and one male patient. The female patients 2 and 11 experienced vaginal spotting during the premenopausal period and patient 5 had vaginal spotting in the middle of the cycle. These blood losses were annoying to the patients but were without complications.

Male patient 8 suffered bleeding from the rectum on the evening of the first day of the study, the cause of which could not be clarified in spite of subsequent intensive gastro-intestinal diagnostic examinations (gastroscopy, colonoscopy,

gastro-intestinal passage with barium meal). The bleeding stopped spontaneously after a few hours and blood transfusions were not necessary.

Discussion

With decreasing renal function, as assessed by CL_{Cr} , the total and renal clearances (CL_{R}) of sulotroban also decreased (Table 2). Renal clearances of the drug were never less than CL_{Cr} suggesting that the compound is excreted by filtration and tubular secretion.

Other pharmacokinetic parameters (Table 2) also changed with increasing impairment of renal function, the most marked differences being in group I.

Enteropathy and metabolic acidosis in the uraemic patient (Mujais *et al.*, 1986) may result in poor absorption of sulotroban and could in part explain the reduced renal recovery of 23.5% in the patients in group I with preterminal renal failure compared with 62.3% of the administered dose in patients with better renal function. However, significant renal excretion beyond 72 h is possible in group I.

Four patients suffered from adverse events, which were without sequelae. The bleeding episodes were observed on the first or second day after administration of the drug, but they did not occur in the patients with the highest values for C_{max} , C_{mean} , AUC or the greatest urinary recovery. They did occur exclusively in patients with the poorest renal function.

The gastro-intestinal bleeding in one male patient was not caused by ulceration in the gastro-intestinal tract that could be demonstrated by endoscopy or X-ray examination. Fine, possibly diffuse, mucosal haemorrhages might, however, have been present. Additive effects of uraemic gastro-enteropathy and thrombocytic disorders of function caused by sulotroban in combination with blocked TXA_2 -dependent vasoconstrictor mechanisms that prevent bleeding are conceivable.

The uterine bleeding from three women was also observed in the course of the first or second day after administration of the study drug. They could be understood causally by similar mechanisms. Sulotroban is a selective antagonist of TXA_2 , but also of prostaglandin $\text{F}_{2\alpha}$ (Stegmeier *et al.*, 1984), which controls the perfusion of the uterine mucosa in equilibrium with prostaglandin E_2 (Chan 1983; Ylikorkala & Mäkilä, 1985). An excess of prostaglandin E_2 caused by sulotroban could lead to diapedetic haemorrhages if the platelet function dependent on TXA_2 is simultaneously blocked.

Table 1 Clinical data of the patients with renal failure

<i>Patient number</i>	<i>Age (years)</i>	<i>Height (cm)</i>	<i>Weight (kg)</i>	<i>Main diagnoses and cause of renal failure (where known)</i>	<i>Creatinine clearance (ml min⁻¹)</i>
1	62	164	66.0	Diabetes mellitus; Hypertension	19
2	51	155	48.5	Bil. cystic kidneys;	12
3	70	173	60	Bil. cirrhotic kidneys; Bechterew's disease; Nephrolithiasis	8
4	44	174	110	Diabetes mellitus; Hypertension	7
5	49	164	83.8	Diabetes mellitus; Hypertension	6
6	77	171	62.1	Diabetes mellitus; Tuberculosis right upper lung	2
7	65	163	61.3	Pyelonephritic cirrhotic kidney, bilateral	4
8	59	183	88	Hypertension; Right nephrectomy because of renal TB***	10.5
9	61	173	85.3	Stroke; Hypertensive crisis; AOD***	47
10*	74	167	66.8	Heart failure; Diabetes mellitus	46
11	47	157	45.3	Recurrent pyelonephritis	36
12	78	170	50.5	Diabetes mellitus; Hypertension	43
13	76	158	43.8	Arterial hypertension; Diabetes mell.; AOD	28
14	77	151	71	Diabetes mellitus; Heart failure	26
15	70	178	70.2	Heart failure; liver cirrhosis;	28
16**	67	177	72.3	Recurrent lung emboli	46
17	52	169	87.5	Congestive cardiomyopathy	33
18	67	154	63.9	Hypertension; Renal arterial stenosis	45
19	79	168	58.2	Diabetes mellitus hypertension	91
20	74	166	72.2	Left heart failure; hypertension; CHD***	60
21	61	163	81.8	Myocardial infarction; Rheumatism	55
22	57	170	84.4	Hypertension; Angina pectoris	98
23	64	163	65.7	Hypertension	84
24	54	169	79.3	Heart failure	52
25	59	175	88.1	Arteriosclerosis, CHD	58
26	58	172	89.2	Chronic urinary obstruction; Myocardial infarction	59

* Patient 10 did not take the tablets

** In patient 16 the experiment was stopped after 24 h

*** Abbreviations: CHD = coronary heart disease; AOD = arterial occlusive disease; TB = tuberculosis

Table 2 Pharmacokinetic parameters (median and range) after administration of 800 mg sulotroban orally once to patients with chronic renal failure (group I–III) and in healthy volunteers (group IV)

	Group I CL_{Cr} 0–20 ml min ⁻¹	Group II CL_{Cr} 21–50 ml min ⁻¹	Group III CL_{Cr} 51–100 ml min ⁻¹	Group IV CL_{Cr} > 100 ml min ⁻¹
C_{max} (mg l ⁻¹)	28.6 (21.7–50.8)	34.3 (15.5–46.1)	18.4 (7.3–30.2)	14.8 (10.6–21.6)
t_{max} (h)	3.5 (2.0–5.0)	1.0 (1.0–2.0)	1.5 (1.0–3.0)	1.0 (0.5–1.5)
AUC (mg l ⁻¹ h)	651.4 (327.2–902.4)	109.5 (37.9–214.5)	47.8 (24.5–88.8)	28.5 (21.1–39.2)
$t_{1/2}$ (h)	18.9 (8.9–39.2)	2.2 (1.3–56.0)	1.3 (1.0–2.1)	1.0 (0.7–2.9)
A _e (% of dose)	23.5 (3.9–61.0)	60.7 (35.5–86.9)	65.9 (48.4–78.4)	62.3 (17.0–82.3)
CL _R (ml min ⁻¹)	6.5 (1.6–20.5)	59.5 (36.9–201.0)	192.2 (103.7–364.7)	317.0 (90.4–519.1)

 C_{max} = Maximum plasma drug concentration t_{max} = Time of maximum plasma drug concentration λ_z = Terminal phase elimination rate constantAUC = Area under the plasma drug concentration-time curve, calculated by the trapezoidal rule with extrapolation to infinity using λ_z $t_{1/2}$ = Half-life calculated from $\ln 2/\lambda_z$ A_e = Amount of unchanged substance in the urineCL_R = Renal clearance calculated from A_e/AUC **Figure 1** Median plasma concentration of sulotroban after a single oral dose of 800 mg. Group I ($\square$ = CL_{Cr} 0 to 20 ml min⁻¹). Group II ($\blacksquare$ = CL_{Cr} 21 to 50 ml min⁻¹), group III ($\circ$ = CL_{Cr} 51 to 100 ml min⁻¹), group IV ($\bullet$ = CL_{Cr} > 100 ml min⁻¹).

Figure 2 Cumulative urinary excretion of sulotroban after a single oral dose of 800 mg (medians; for symbols see legend to Figure 1) in the presence of different degrees of renal failure.

Figure 3 Relationship between AUC and CL_{Cr} after a single oral dose of 800 mg sulotroban ($y = 5666/x - 18.0$; $r = 0.93$).

Figure 4 Dose adjustment according to the degree of renal failure from $AUC\ g/AUC \times 100$. Single oral dose of 800 mg sulotroban ($y = 0.877x - 0.619$; $r = 0.89$).

On the basis of the present results, a tentative recommendation for dose adjustment in relation to creatinine clearance may be suggested. In Figure 4 the adjusted dose is shown as the percentage of the standard dose that is necessary to obtain the same AUC as in average healthy volunteers at the given creatinine clearance. Because of the variability in AUC, dose reduction

does not appear to be necessary above a creatinine clearance of 50 ml min^{-1} . In patients with moderately restricted renal function and creatinine clearances of $< 50\text{ ml min}^{-1}$ but $> 20\text{ ml min}^{-1}$, a dose reduction to 20–40% may be appropriate. In patients with severe renal failure ($\leq 20\text{ ml min}^{-1}$), the dose should be reduced to $< 20\%$ of normal.

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