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Hemostasis in Patients with Normal and Impaired Renal Function Under Treatment with Cefodizime

Summary: Ten patients (two with normal, eight with impaired renal function) on their usual diet were treated with cefodizime (HR 221) for seven days. The dosage was 4 g/day, adapted to renal function as appropriate. Platelet function, plasma coagulation and vitamin K metabolism were investigated before and on day 7 of therapy. Platelet function and plasma coagulation remained unchanged, regardless of the size of the serum antibiotic trough levels, in both normal and impaired renal function. Vitamin K_1 metabolism remained unaffected, since no increase in vitamin K_1 2,3 epoxide in the circulation was observed during the therapy. Cefodizime (HR 221), a parenteral aminothiazole cephalosporin, does not affect hemostasis.

Zusammenfassung: *Einfluß von Cefodizim (HR 221) auf die Hämostase.* Zehn Patienten (zwei mit normaler, acht mit eingeschränkter Nierenfunktion) wurden sieben Tage mit Cefodizim (HR 221), einem parenteralen Aminothiazol-Cephalosporin, behandelt. Die Dosierung wurde der Nierenfunktion angepaßt. Thrombozytenzahl, Thrombozytenfunktion und Blutungszeit, plasmatische Gerinnung und Vitamin-K-Metabolismus wurden vor und am Tag 7 der Therapie mit Cefodizim untersucht. Unabhängig von den Antibiotikaspiegeln blieb die Hämostase bei Patienten mit normaler und eingeschränkter Nierenfunktion unbeeinflußt. Weder Plättchenfunktion noch plasmatische Gerinnung änderten sich signifikant. Der Vitamin-K-Metabolismus wurde nicht beeinträchtigt.

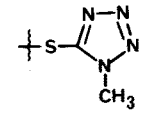
Introduction

Hemorrhage is a well known complication of therapy with β-lactam antibiotics. Bleeding problems occur more commonly in patients with impaired renal function, elderly patients and malnourished patients receiving parenteral nutrition. The basic mechanisms involved are platelet dysfunction and a plasma coagulation defect. Platelet dysfunction is caused by interference with platelet membrane receptors and is evaluated by measurement of bleeding time and aggregation in response to aggregating agents, especially adenosine diphosphate (ADP) and epinephrine. The plasma coagulation defect is caused by interference with vitamin K-dependent clotting factors and evaluated by measurement of prothrombin time (PT) and partial thromboplastin time (PTT).
All antibiotics bearing a N-methyl-thio-tetrazole (NMTT) side chain (Figure 1 a) interrupt the hepatic vitamin K epoxide cycle by inhibiting vitamin K epoxide reductase (1). However, cefazoline, an example of a cephalosporin bearing a different heterocyclic thio function in 3'-position, namely a 5-methyl-1,3,4-thiadiazole-2-thio moiety (Figure 1 b), also causes alteration of the plasma coagulation system (2, 3). Cefodizime (HR 221) is a new aminothiazole cephalosporin with a broad spectrum of activity covering gram-positive and gram-negative bacteria (4, 5, 6). The activity against anaerobic bacteria resembles that of cefotaxime. Cefodizime is mainly excreted via the kidney. As cefodizime is substituted by a 1,3-thiazole-2-thio group in 3'-position (Figure 2), the purpose of the following study was to investigate hemostasis in patients with various degrees of renal insufficiency under treatment with this antibiotic.

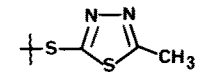
Patients and Methods

After informed consent had been obtained, ten patients (six female, four male), median age 51 years, range 23 to 75 years with

a) **Cephalosporin residue**

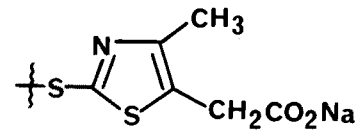


N-Methyl-tetrazole-thio (NMTT) side chain



b) **Methyl-thiadiazole-thio side chain**

Figure 1: a) N-methylthiotetrazole side chain as present in latamoxef and cefoperazone. b) 5-methyl-1,3,4-thiadiazole-2-thio side chain as present in cefazoline.



side chain of Cefodizime

Figure 2: 4-methyl, 5-carboxymethyl, 1,3-thiazole-2-thio side chain as present in cefodizime (HR 221).

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Table 1: Patients treated with cefodizime.

Patients No.	Age (years)	Sex	Serum creatinine (mg/dl)	Creatinine clearance (ml/min)	Parenteral nourishment	Indication	Dosage (g/day)	HR 221 serum trough level (mg/l)
1	36	f	3.3	19	none	UTI[+]	2	27.8
2	58	m	11.4	1	none	RTI[++]	1	44.0
3	50	f	1.7	36	none	RTI	4	55.0
4	75	m	1.6	32	none	RTI	4	52.0
5	46	f	1.1	92	none	UTI	4	33.0
6	58	m	8.1	8	none	RTI	2	87.0
7	65	f	1.9	24	none	RTI	4	92.0
8	46	m	0.7	120	none	UTI	4	17.0
9	23	f	1.3	54	none	UTI	4	37.0
10	52	f	1.3	59	none	UTI	4	20.0

[+] UTI = urinary tract infection; [++] RTI = respiratory tract infection.

confirmed infections and clinical indications for cephalosporin therapy were treated with cefodizime (HR 221, Hoechst AG). As calculated by creatinine clearance two patients had normal renal function and eight had impaired renal function. Three patients were immunocompromised due to concomitant immunosuppressive therapy (two kidney transplant patients, one patient with systemic lupus erythematosus), one patient was on hemodialysis. All patients had normal liver function as evaluated by measurement of transaminases. The relevant clinical data are given in Table 1. The dose regimen was adjusted according to the degree of renal impairment as follows:

a) Normal renal function: 4 g/day;

b) Moderate renal impairment (serum creatinine below 3 mg/dl and creatinine clearance above 25 ml/min): 4 g/day;

c) Severe renal impairment (serum creatinine 3–8 mg/dl and creatinine clearance 25–10 ml/min): 2 g/day;

d) Uremia or hemodialysis (serum creatinine above 8 mg/dl and creatinine clearance below 10 ml/min): 1 g/day.

None of the patients was receiving drugs known to interfere with platelet function, plasma coagulation, and vitamin K metabolism. All patients were on their usual diets. The antibiotic was administered for seven days. The following exclusion criteria applied: concurrent antibacterial therapy, a high probability of change in renal function during the observation period; platelet dysfunction before therapy, with the exception of changes due to the underlying renal disease; history of penicillin or cephalosporin sensitivity; infections known to be resistant to cefodizime.

Assessment of hemostasis: Platelet function, plasma coagulation and vitamin K metabolism were analysed before and on day 7 of therapy at antibiotic serum trough levels.

a) Platelet counts, bleeding time and platelet aggregation (300,000/µl) with ADP (10^{-6}M), collagen (10^{-6} g/ml), epinephrine (10^{-6M}), ristocetin (1 mg/ml) with evaluation of maximal amplitude were investigated as published previously (7).

b) Plasma coagulation was analysed by measurement of prothrombin time, partial thromboplastin time and decarboxyprothrombin (PIVKA II) as published previously (7).

c) Vitamin K 1 metabolism: Vitamin K_1 2,3 epoxide in plasma, as an indicator of a coumarin-like inhibition of hepatic vitamin K metabolism, was measured in five patients before and 2, 4 and 6 h after an i.v. bolus of 10 mg vitamin K_1 (Konakion®) with electron-capture gas-liquid capillary chromatography according to *Bechtold* et al. (8). The area under the curve (AUC) of vitamin K_1 epoxide was evaluated by the trapezoidal rule.

Antibiotic serum trough levels: Drug serum levels were measured by high performance liquid-chromatography according to *Uihlein* et al. (9). Detection limit was 0.4 mg/l. Error of the method is 5%. Serum levels are given as a mean of two determinations performed on days 3 and 7 of therapy.

Statistics: A non-paired statistical test was used (Wilcoxon test).

Results

As shown in Table 2, at serum antibiotic concentrations in and above the therapeutic range, there were no significant changes in platelet count, platelet aggregation or bleeding time during therapy.

Table 2: Hemostasis in patients treated with cefodizime (HR 221) (n = 10) (median and range).

	Bleeding time (sec)	Platelet counts (mm^3)	Platelet aggregation (maximum amplitude) ADP (%)	collagen (%)	epinephrine (%)	ristocetin (%)	PT (sec)	PTT (sec)	HR 221 serum trough level (mg/l)	K_1 2,3 epoxide AUC (0–6h) µg.h.ml^{-1}
DAY 0	303 (181–740)	222,000 (72,000–271,000)	38 (24.1–32.6)	48.1 (21.9–76.9)	14.4 (10–32.5)	56.3 (32.5–68.8)	12.2 (12–13.5)	26.7 (24.8–32.6)	–	–
DAY 7	252 (133–534)	240,000 (175,000–369,000)	44.2 (27.5–66.3)	57.8 (43.8–84.4)	17.1 (6.3–31.2)	53.8 (48.4–76.3)	12.3 (12.1–13.5)	28.3 (24.8–31.6)	40 (17–92)	< 0.1

The plasma coagulation, evaluated by measurement of prothrombin or partial thromboplastin times, remained unchanged. There was no indication that vitamin K-dependent clotting factors were affected, since decarboxyprothrombin (PIVKA II) was never demonstrated in the circulating blood. Vitamin K_1 2,3 epoxide remained constantly below the upper cut off point of 30 ng/ml (10); in addition the AUC 0–6 h of vitamin K_1 2,3 epoxide was always below 0.1 $\mu g.h.ml^{-1}$.

Adverse effects

The drug was well tolerated by all patients. No side effects were observed with the exception of one patient who had loose stools. No disturbance of renal function or hepatic function was seen. No hematological side effects were observed. The clinical efficacy was good with improvement or cure in all patients.

Discussion

Bleeding tendency is a well known and recognized side effect of treatment with β-lactam antibiotics. Synthetic penicillin derivatives (with the exception of isoxazolyl penicillins) can cause platelet dysfunction, whereas cephalosporins which affect hemostasis mainly cause a plasma coagulation disorder. However, there are some exceptions to this general rule since some cephalosporins – latamoxef and cefoperazone (7) – have been shown to disturb both platelet function and plasma coagulation. Platelet dysfunction is best investigated by the concomitant measurement of bleeding time and platelet aggregation in response to exogenously added agents. The presence of a plasma coagulation disorder should be determined by measurement of prothrombin time and partial thromboplastin time. In addition, sensitive indicators of altered vitamin K metabolism should be investigated, because disturbed plasma coagulation is mainly seen in the critically ill patients. The most sensitive test available for the evaluation of vitamin K metabolism is the detection of circulating vitamin K_1 2,3 epoxide in plasma after i.v. administration of 10 mg vitamin K_1. The presence of circulating precursors of coagulation factors which are released into the circulation in absence of vitamin K is a further indicator of impaired vitamin K metabolism. A disturbance of vitamin K metabolism has been reported for cephalosporins bearing a 1-methyl-tetrazole-5-thio side chain (11). However, cephalosporins bearing other heterocyclic thio functions also have this property, and it is therefore an oversimplication to say that impairment of vitamin K metabolism is caused only by NMTT (11). Cefodizime is a new cephalosporin with a 1,3-thiazole-2-thio rest in 3′-position, substituted by a 4-methyl and a 5-carboxymethyl group. Since cefodizime, in contrast to cefazoline, does not lead to an increase in vitamin K_1 2,3 epoxide in plasma – independent of the serum antibiotic trough levels – either the 1,3-thiazole ring itself or one or both of its chemical substituents seem to be responsible for the absence of effect of cefodizime on the vitamin K epoxide cycle. Platelet function was also unaltered under treatment with cefodizime. It has been postulated that the additional carboxylic group in the 7-acyl chain in latamoxef, a 1-oxacephalosporin, might be responsible for the platelet defect (12). Our investigation clearly demonstrates that the simple presence of a second carboxylic group in a cephalosporin does not necessarily confer the ability to induce a platelet defect.

Conclusion

Hemostasis was not affected by treatment with cefodizime in patients with normal or impaired renal function.

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