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Differential Effect of Impaired Renal Function on the Kinetics of Clavulanic Acid and Amoxicillin

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Amoxicillin and clavulanic acid are prescribed as a fixed drug combination. The purpose of the present study was to assess the influence of various degrees of renal insufficiency (glomerular filtration rate [GFR], <5 to >75 ml/min per 1.73 m^2) on the pharmacokinetics of amoxicillin and clavulanic acid following oral (500 and 125 mg of amoxicillin and clavulanic acid, respectively) and intravenous (1,000 and 200 mg, respectively) dosing. The volume of distribution and the systemic availability were independent of the renal function, while the total body clearance and the renal and the nonrenal clearance of amoxicillin and clavulanic acid decreased with decreasing renal function. The decrease in the total body clearance was more pronounced for amoxicillin than for clavulanic acid. This explains the increase in the ratio of the area under the plasma concentration versus time curve of amoxicillin to that of clavulanic acid with decreasing glomerular filtration rate after oral dosing; for example for a GFR of 75 ml/min, the ratio of amoxicillin to clavulanic acid was 4.9 ± 1.2; for a GFR of 35 to 75 ml/min, 5.3 ± 2.4; for a GFR of 10 to 35 ml/min, 11.9 ± 5.8; for a GFR of 5 to 10 ml/min, 13.4 ± 9.1; and for patients on hemodialysis, 14.7 ± 5.3. Dosage recommendations are suggested which prevent undue accumulations of amoxicillin while maintaining adequate concentrations of clavulanic acid.

The antibacterial activity of amoxicillin depends on the inhibition of enzymes concerned with the construction of the bacterial cell wall. In many bacteria these enzymes might have in their vicinity β-lactamases, which can inactivate amoxicillin (12, 15, 21). Clavulanic acid inhibits many of these β-lactamases in vitro (9, 14, 16–18, 23). In vivo the combined administration of amoxicillin and clavulanic acid extends the spectrum of amoxicillin to embrace β-lactamase-producing strains such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Bacteroides fragilis*, and *Staphylococcus aureus* (1, 2, 4, 8, 11).

Ideally, the use of a fixed drug combination in patients with diseases of organs responsible for the metabolism or excretion of these drugs or both would require that the elimination rate of each agent be affected to the same extent, what practically never occurs. The objective of the present study, therefore, was to assess the changes in the pharmacokinetics of amoxicillin and clavulanic acid in patients with impaired renal function and hence to allow dosage adjustments to be predicted for these patients.

MATERIALS AND METHODS

The total number of subjects was 35 (12 female, 23 male); 6 were normal healthy volunteers with normal renal function, 12 were maintained on intermittent hemodialysis, and the remaining 17 had various degrees of impaired renal function. The patients were divided into five groups, according to their renal function. Group 1, creatinine clearance, >1.3 ml/min · kg (>75 ml/min per 1.73 m^2); age range, 22 to 26 years; median age, 25 years; sex, two females and four males. Group 2, ^{51}Cr EDTA clearance rate, 0.52 to 1.10 ml/min · kg (35 to 75 ml/min per 1.73 m^2), age range, 39 to 74 years; median age, 56 years; sex, 1 female and five males. Group 3, ^{51}Cr EDTA clearance rate, 0.16 to 0.39 ml/min · kg (10 to 35 ml/min per 1.73 m^2); age range, 34 to 71 years; median age, 50 years; sex, four females and two males. Group 4, creatinine clearance, 0.07 to 0.16 ml/min · kg (5 to 10 ml/min per 1.73 m^2); age range, 57 to 75 years; median age, 67 years; sex, five males. Group 5, patients on maintenance hemodialysis; age range, 22 to 75 years; median age, 51 years; sex, seven males and five females. Informed consent was obtained before initiation of the study. The study was approved by the Committee on Human Research, University of Bern.

All subjects participated in an intravenous (i.v.) and oral (p.o.) study, and the sequence of i.v. or p.o. administration was chosen at random. Amoxicillin-clavulanic acid (Augmentin; Beecham Pharmaceutical Chemotherapeutic Research Centre) was either injected by a bolus i.v. infusion over 30 s (1 g of sodium amoxicillin, 200 mg of potassium clavulanate diluted in 20 ml of sterile water) or supplied as a film-coated tablet (500 mg of amoxicillin trihydrate, 125 mg of potassium clavulanate). A minimum of 1 week elapsed between the first and the subsequent administration of the drug in all subjects. The subjects fasted from food and fluid from 11 p.m. the previous evening. Immediately after dosing, all subjects received 200 ml of water. Two hours later they were given a light fatless breakfast and another 20 ml of liquid (no caffeine, no milk, no cream). A further 200 ml of liquid was administered at 4 h. Food and fluid had been restricted for 6 h. In patients on maintenance hemodialysis, fluid intake was restricted as usual.

Blood and urine collection. (i) Group 1. For the formulation administered p.o., blood samples (5 ml) were obtained before dosing and at 20, 40, 60, and 90 min and after 2, 4, 5, 6, 10, 12, and 24 h after the dose. For the dose administered i.v. blood samples were taken before dosing and at 5, 10, 15, 20, 30, 45, 60, and 90 min and at 2, 3, 4, 6, and 8 h after the dose. Urine was collected from 0 to 4 and from 4 to 8 h.

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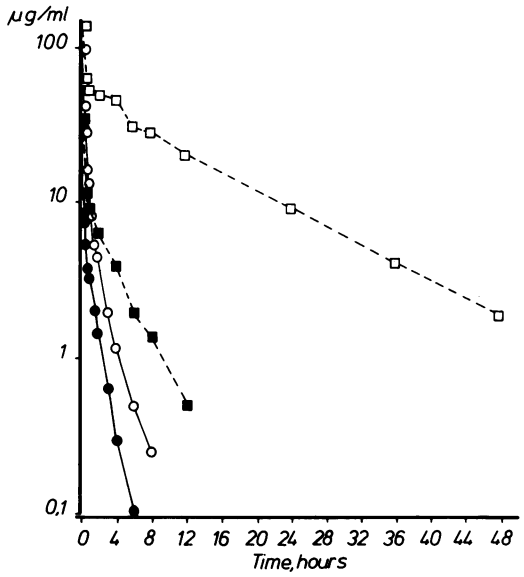

FIG. 1. Plasma concentration-time curve of clavulanic acid (●) and amoxicillin (○) after i.v. dosing in a subject with normal renal function (GFR, 104 ml/min per 1.73 m^2). Plasma concentration-time curve of clavulanic acid (■) and amoxicillin (□) after i.v. dosing in a patient with impaired renal function (GFR, 4.8 ml/min per 1.73 m^2).

(ii) Groups 2, 3, and 4. For the p.o. formulation blood samples were obtained as described above for group 1. Two additional blood samples were obtained from all three groups at 36 and 48 h after the dose. Five urine samples were collected at 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 36 h. In groups 3 and 4 urine was also collected at 36 to 48 h. For the i.v. dose, blood samples were taken at 0, 5, 15, 30, 60, and 90 min and at 2, 3, 4, 6, 8, and 12 h after the dose. Additional samples were obtained at 24 h (groups 3 and 4) and at 36 and 48 h (group 4). Urine was collected from 0 to 4, 4 to 8, and 8 to 12 h (groups 2, 3, and 4), 12 to 24 h (groups 3 and 4) and 24 to 36 and 36 to 48 h (group 4).

(iii) Group 5. The patients on hemodialysis were given the drugs 6 h prior to initiation of a 4-h hemodialysis period. Blood samples were collected as described above for group 4. In addition, hourly collections were performed during the hemodialysis period. No urine was collected. Plated or coiled artificial kidneys were used with a constant blood flow rate of 200 to 275 ml/min and a dialysate flow rate of 500 ml/min.

Antibiotic assays. Blood samples were left to clot for 30 min and then centrifuged for 10 min. Urine specimens were diluted 10-fold in 0.1 M citrate buffer (pH 6.5) immediately after collection. Serum and urine samples were frozen at −70°C. Each sample of serum and urine was assayed for both amoxicillin and clavulanic acid by the microbiological assay unit at Beecham by standard microbiological techniques (10). The limit of detection for amoxicillin and clavulanic acid was 0.02 and 0.08 μg/ml, respectively. The interday variability for amoxicillin and clavulanic acid was 6.35 and 7.61%, respectively, in serum and 5.32 and 6.46%, respectively, in urine.

Pharmacokinetic analysis. (i) Compartment-independent analysis. Model- (compartment) independent evaluation of the kinetic data was completed for each subject (3). Estimates of total body clearance (CL) and volume of distribution at steady-state (V_{ss}) were calculated using

$$CL = \frac{Dose}{AUC} \quad (1)$$

$$V_{ss} = \frac{Dose \times AUMC}{AUC^2} \quad (2)$$

where AUC is the area under the concentration-time curve to infinity and AUMC is the area under the first moment of the plasma concentration-time curve. The AUC was calculated by the trapezoidal rule. The terminal area was calculated as

$$\frac{C \cdot t_{1/2}}{\ln 2} \quad (3)$$

where C is the last plasma concentration assessed and $t_{1/2}$ is the terminal half-life. Renal clearance (CL_R) values were calculated by dividing the amount of unchanged drug recovered in urine by the corresponding AUC. The nonrenal clearance (CL_{NR}) values were obtained by subtracting the CL_R from the CL values. The systemic availability from the dose administered p.o. ($D_{p.o.}$) was calculated from the ratio of the AUC after the dose administered p.o. ($AUC_{p.o.}$) to the AUC from the dose administered i.v. ($AUC_{i.v.}$) as follows:

$$\frac{AUC_{p.o.} \times D_{i.v.}}{AUC_{i.v.} \times D_{p.o.}} \quad (4)$$

The patients investigated in this study had no clinical or anamnestic evidence of liver disease. In 7 patients and 3 normal subjects the galactose elimination capacity was measured by the method of Tygstrup (22).

(ii) Statistical analysis. Comparisons were made by using Student's unpaired t test. In case of multiple comparisons

TABLE 1. Pharmacokinetic parameters of amoxicillin

Parameter	Group 1	Group 2	Group 3	Group 4
GFR				
ml/min per 1.73 m^2	>75	35–75	10–35	5–10
ml/min per kg	>1.3	0.52–1.10	0.16–0.39	0.03–0.16
CL, ml/min per kg	3.65 ± 1.01	1.50 ± 0.42	0.64 ± 0.15	0.34 ± 0.07
CL_R ml/min per kg	2.60 ± 0.82	1.15 ± 0.29	0.31 ± 0.15	0.11 ± 0.07
CL_{NR} ml/min per kg	1.05 ± 0.30	0.35 ± 0.19	0.33 ± 0.05	0.23 ± 0.06
V_{ss}, liter/kg	0.29 ± 0.06	0.27 ± 0.13	0.23 ± 0.06	0.22 ± 0.03
Systemic bioavailability, %	57 ± 19	77 ± 13	76 ± 11	69 ± 7
$t_{1/2}$ (β-phase), h	1.95 ± 0.42	2.26 ± 0.48	4.58 ± 1.39	10.12 ± 1.44[a]
Urinary excretion, % of i.v. dose	71 ± 6	77 ± 9	46 ± 13	33 ± 13

[a] Mean of five determinations.

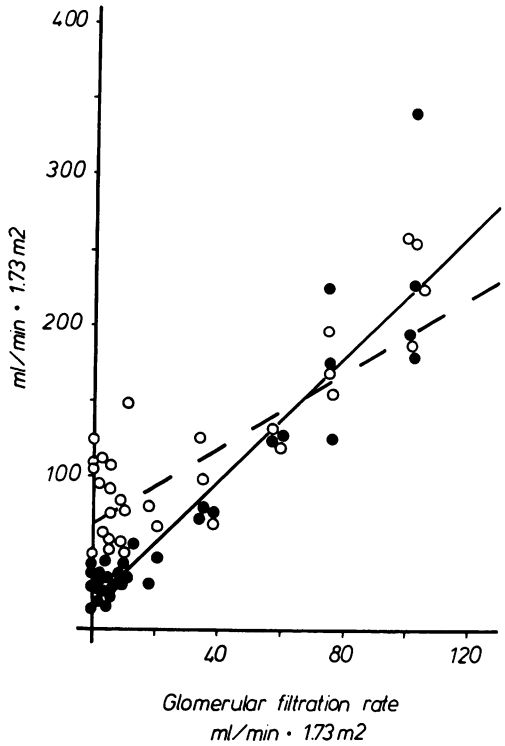

FIG. 2. CL of amoxicillin (●) or clavulanic acid (○) and GFR. The linear regression of amoxicillin and clavulanic acid was as follows: $y = 2.27(GFR + 13)$ ($r = 0.94$; $P < 0.001$); $y = 1.45(GFR + 69)$ ($r = 0.76$; $P < 0.001$). Note that the decline in the CL of amoxicillin was more pronounced than that of clavulanic acid.

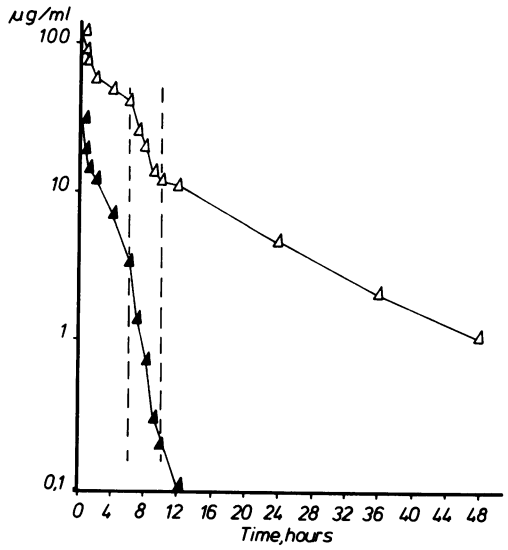

FIG. 3. Influence of hemodialysis treatment on the concentrations of clavulanic acid (▲) and amoxicillin (△) in plasma in a representative patient. At the end of dialysis, no clavulanic acid was measurable but amoxicillin was.

corrections were performed. Results are reported as mean ± standard deviation.

RESULTS

Amoxicillin. Results shown in Fig. 1 demonstrate that the concentrations of amoxicillin in plasma 4 h after dosing were about 10 times higher in a subject with severely impaired renal function (glomerular filtration rate [GFR], < 10 ml/min per 1.73 m^2) compared with those in a normal subject. When all subjects were analyzed as a group, the CL of amoxicillin decreased with decreasing renal function (Table 1 and Fig. 2). The decrease in CL was mainly attributable to a decrease in the CL_R (Table 1). When all subjects were analyzed together, the CL_{NR} of amoxicillin decreased linearly with decreasing GFR ($r = 0.83$; $P < 0.001$; Table 1). The systemic bioavailability of amoxicillin was about 70% and independent of the renal function (Table 1). The V_{ss} did not change as a function of the GFR. In normal volunteers the $t_{1/2}$ (β-phase) of amoxicillin was 1.95 ± 0.42 h (mean ± standard deviation). In patients on maintenance hemodialysis the mean $t_{1/2}$ on ($n = 10$) and off ($n = 11$) dialysis was 2.43 ± 0.29 and 12.63 ± 3.63 h, respectively (Fig. 3).

Clavulanic acid. The concentrations of clavulanic acid in plasma increased with declining renal function (Fig. 1 and Table 2). The decrease in CL with decreasing renal function was attributable to a decrease in both CL_R and CL_{NR} (Table 2 and Fig. 2). The systemic bioavailability of clavulanic acid was about 50% (Table 2). The bioavailability and the V_{ss} values were independent of the renal function. In normal volunteers the $t_{1/2}$ of clavulanic acid was 1.25 ± 0.23 h. In patients on maintenance hemodialysis the mean $t_{1/2}$ on ($n = 8$) and off ($n = 7$) dialysis were 1.24 ± 0.19 h and 3.81 ± 0.88 h, respectively (Fig. 3).

Despite the lower systemic bioavailability of clavulanic acid than of amoxicillin, the mean ratio of the AUCs of amoxicillin to clavulanic acid for all subjects investigated was not different after p.o. than after i.v. dosing (Table 3).

TABLE 2. Pharmacokinetic parameters of clavulanic acid

	Group 1	Group 2	Group 3	Group 4
GFR				
ml/min per 1.73 m^2	>75	35–75	10–35	5–10
ml/min per kg	>1.3	0.52–1.10	0.16–0.39	0.03–0.16
CL, ml/min per kg	3.45 ± 0.39	1.74 ± 0.42	1.24 ± 0.59	1.04 ± 0.27
CL_{LR}, ml/min per kg	0.98 ± 0.51	0.55 ± 0.21	0.15 ± 0.08	0.06 ± 0.03
CL_{NR}, ml/min per kg	2.33 ± 0.38	1.19 ± 0.26	1.09 ± 0.60	0.96 ± 0.23
V_{ss}, liter/kg	0.22 ± 0.06	0.20 ± 0.02	0.18 ± 0.05	0.22 ± 0.04
Systemic bioavailability, %	45 ± 12	75 ± 24	44 ± 19	61 ± 29
$t_{1/2}$ (β-phase), h	1.25 ± 0.23[a]	1.50 ± 0.53	2.45 ± 0.49[b]	3.30 ± 0.78
Urinary excretion, % of i.v. dose	35 ± 7	32 ± 6	16 ± 5	8 ± 3

[a] Mean of four determinations.
[b] Mean of five determinations.

TABLE 3. Ratio of $AUC_{amoxicillin}/AUC_{clavulanic\ acid}$[a]

Group (GFR [ml/min per 1.73 m^2])	$AUC_{amoxicillin}/AUC_{clavulanic\ acid}$ for the following doses[b]:	
	p.o.	i.v.
1 (>75)	4.98 ± 1.15	4.77 ± 1.10
2 (35–75)	5.32 ± 2.39	6.09 ± 1.42
3 (10–35)	11.86 ± 5.76	8.67 ± 3.24
4 (5–10)	13.36 ± 9.08	12.78 ± 3.96
5 (hemodialysis)	14.70 ± 5.30	11.87 ± 4.05

[a] AUC denotes $AUC_{0-\infty}$.
[b] Values are the mean ± standard deviation after a p.o. and an i.v. dose.

This is explained by the lower ratio of clavulanic acid to amoxicillin in the i.v. than in the p.o. formulation.

Ratio of amoxicillin to clavulanic acid in plasma. In subjects with normal renal function the amoxicillin concentrations after p.o. or i.v. doses were about 5 times higher than the clavulanic acid concentrations (Table 3 and Fig. 1). This ratio increased from about 5 to 12 as renal function declined (Table 3 and Fig. 1). The AUCs used for the calculation of the patients in group 5 (patients on maintenance hemodialysis) were derived from the entire plasma concentration-time curve, including also the hemodialysis period.

Urinary excretion data for clavulanic acid and amoxicillin after a p.o. or i.v. dose are given in Tables 4 and 5. In subjects with renal impairment (groups 2 to 4) concentrations of clavulanic acid and amoxicillin in urine were higher and more prolonged than those seen in subjects with normal renal function (group 1). This was also reflected in the concentrations observed in plasma (Fig. 1).

The median of the galactose elimination capacity measured in seven patients with renal failure was 3.5 mg/min per kg (range, 4.1 to 4.9 mg/min per kg). The values in the three normal volunteers were 6.5, 7.0, and 7.2 mg/min per kg. The normal values for galactose elimination capacity at the University of Bern are 6 to 10 mg/min per kg (M. Heri, Ph.D. dissertation, University of Bern, Bern, Switzerland, 1979).

DISCUSSION

In the present study, as renal failure progressed, the CL_R of amoxicillin and clavulanic acid fell as expected. The CL_{NR} was also lower in patients with renal failure compared with that in healthy volunteers. This difference cannot be explained by the lower mean age of the normal volunteers, because patients with various degrees of impaired renal function were about the same age as normal volunteers (i.e., the youngest patients) and had lower CL_{NR} values than the healthy controls. In some patients with impaired renal function, the liver function was assessed by measuring the galactose elimination capacity (22; Heri, Ph.D. dissertation). Despite the absence of clinical and anamnestic evidence of liver disease, many of these patients had a galactose elimination capacity that was either decreased or in the low normal range, indicating impaired liver function. A similar decline (as for clavulanic acid and amoxicillin) in the nonrenal elimination of unchanged drug, in the presence of renal failure, has been reported previously for procainamide (7).

In subjects exhibiting normal renal function the urinary excretion of unchanged amoxicillin and clavulanic acid following p.o. administration was 56 and 22%, respectively. These results confirm the urinary excretion values of amoxicillin (54%) and clavulanic acid (31%) in normal volunteers reported by Saito (19). Compared with clavulanic acid, the fraction of amoxicillin excreted unchanged in urine following i.v. administration was thus higher by a factor of 1.7 to 2.5 (Table 1) (19). Therefore, one would predict that the ratios of amoxicillin to clavulanic acid in plasma would also be higher by a factor of 1.7 to 2.5 in patients with a GFR close to zero (groups 4 and 5) when compared with subjects exhibiting a normal renal function (group 1). However, the measured ratios were even slightly higher (2.5 to 3 times) in patients with severely impaired renal function than in subjects with normal renal function (Table 3). This discrepancy between the predicted and the measured values is best explained by the more pronounced reduction in the CL_{NR} of amoxicillin than of clavulanic acid in patients with (groups 2 to 4) than in patients without (group 1) renal failure (Tables 1 and 2).

The increase in the ratio of AUCs of amoxicillin to clavulanic acid with decreasing renal function (Table 3) resulted from the greater attenuation in pharmacokinetics of amoxicillin than of clavulanic acid. V_{ss} for both compounds was unaffected by renal impairment but mean CL for amoxicillin was reduced by more than 90% between groups 1 and 4, while the mean reduction for clavulanic acid was about 70%. This was an expected finding, since in subjects

TABLE 4. Urinary excretion of clavulanic acid and amoxicillin after p.o. dosing

Hour	Drug[a]	Urinary excretion (μg/ml) for:			
		Group 1	Group 2	Group 3	Group 4
0–4	C	123.1 ± 44.2	91.5 ± 53.2	10.7 ± 11.9	13.7 ± 6.7
	A	1,046.9 ± 231.0	580.7 ± 347.3	142.0 ± 103.0	88.5 ± 55.5
4–8	C	18.7 ± 18.3	36.3 ± 36.8	7.6 ± 3.9	11.2 ± 5.9
	A	487.4 ± 484.0	467.2 ± 310.0	215.5 ± 152.4	119.2 ± 45.1
8–12	C	0.5 ± 0.5[b]	9.5 ± 11.8	1.9 ± 0.7	4.7 ± 2.3
	A	14.4 ± 10.6[b]	150.0 ± 92.5	101.2 ± 87.2	85.1 ± 19.3
12–24	C		<0.08	0.29 ± 0.15	1.2 ± 1.4[c]
	A		14.5 ± 5.7	40.0 ± 26.8	50.1 ± 21.8
24–36	C	ND[d]	ND	<0.08	<0.08
	A	ND	2.3 ± 3.4	7.8 ± 6.3	14.3 ± 8.3
36–48	C	ND	ND	<0.08	<0.08
	A	ND	ND	1.3 ± 0.9	6.0 ± 3.9

[a] C, Clavulanic acid; A, amoxicillin.
[b] Values are from urine collected in group 1 from 8 to 24 h.
[c] One subject had nonmeasurable concentrations (<0.1 μg/ml)
[d] ND, Not determined.

TABLE 5. Urinary excretion of clavulanic acid and amoxicillin after i.v. dosing

Hour	Drug[a]	Urinary excretion (μg/ml) for:			
		Group 1	Group 2	Group 3	Group 4
0–4	C	403.4 ± 234.8	265.9 ± 155.4	66.4 ± 36.3	41.9 ± 15.9
	A	4,185.3 ± 2637.1	2429 ± 1,902.0	705.0 ± 436.0	434.6 ± 191.3
4–8	C	21.0 ± 10.9	52.4 ± 50.5	21.2 ± 14.1	18.8 ± 12.1
	A	241.3 ± 76.5	781.4 ± 596.0	396.2 ± 276.8	389.0 ± 186.5
8–12	C	ND[b]	12.3 ± 9.9	6.9 ± 7.3	11.1 ± 9.3
	A	ND	310.7 ± 138.0	187.5 ± 134.4	385.0 ± 266.3
12–24	C	ND	ND	3.0 ± 5.2	1.7 ± 1.8
	A	ND	ND	75.9 ± 47.7	151.2 ± 90.0
24–36	C	ND	ND	ND	<0.08
	A	ND	ND	ND	46.5 ± 25.8
36–48	C	ND	ND	ND	<0.08
	A	ND	ND	ND	19.5 ± 8.8

[a] C, Clavulanic acid; A, amoxicillin.
[b] ND, Not determined.

with normal renal function the mean CL_R accounted for only 28% of the mean CL of clavulanic acid, while the corresponding value for amoxicillin was 71% (Tables 1 and 2, group 1). The CL_R of amoxicillin was higher than the GFR, indicating that amoxicillin, like other penicillins (6), is largely secreted by the tubules. The ratios of AUCs indicate the relative change in pharmacokinetics with renal impairment, although they are not of significance for antimicrobial activity and therapeutic efficacy, which depend on absolute concentrations of amoxicillin and clavulanic acid.

During hemodialysis, the $t_{1/2}$ values of both agents approached those determined in subjects with normal renal function. The high hemodialysis clearance of amoxicillin and clavulanic acid can be explained by the low molecular weight, a binding to plasma proteins of less than 30%, and a low V_{ss} (13, 20).

Dosage recommendations. The V_{ss} values of amoxicillin and clavulanic acid were independent of the renal function; thus, no dosage adjustment is required for the initial loading dose for patients with renal impairment. Since the systemic availability of amoxicillin and clavulanic acid are independent of renal function, the adjustment for the maintenance dose made for patients with reduced renal function is similar for p.o. as for i.v. administration and can be performed on the basis of CL. The results from this study indicate that the CL of amoxicillin is reduced as renal function decreases to a much greater extent than that of clavulanic acid. Since clavulanic acid and amoxicillin are marketed as a fixed drug combination, dosage adjustments must be performed on the basis of the pharmacokinetics of clavulanic acid and not of amoxicillin, to avoid underdosage of clavulanic acid in patients with renal failure. The drawback of this approach is an overtreatment with amoxicillin. If the peak concentration, the trough, and the average concentration of clavulanic acid must be the same in patients with impaired renal function as in compromised patients, then the dose of clavulanic acid must be kept constant while the dosing interval (τ) must be changed as follows (5):

$$\tau_{ren} = \tau_{norm}\left[\frac{218}{1.45(GFR + 69)}\right] \quad (5)$$

where τ_{norm} and τ_{ren} are the dosing interval in normal subjects and in patients with impaired renal function, respectively. Drug intervals for clavulanic acid should not exceed 12 h to avoid long durations of subtherapeutic concentrations of clavulanic acid in plasma. In the event that the dose rather than the dosing interval is changed, then the following equation for clavulanic acid can be used (5):

$$D_{ren} = D_{norm}\left[\frac{1.45(GFR + 69)}{218}\right] \quad (6)$$

where D_{ren} and D_{norm} represent the doses in renal and normal subjects, respectively.

For a standard dosage regimen of 1,000 mg of amoxicillin–200 mg of clavulanate given i.v. or 500 mg of amoxicillin–125 mg of clavulanate given p.o. evey 4 h to patients with normal renal function, although the loading dose should be unchanged, we recommend the maintenance dose or the dosage interval or both as follows. Patients with a GFR of >75 ml/min per 1.73 m^2 and patients with a GFR of between 35 and 75 ml/min per 1.73 m^2 should be given the standard dose every 4 and every 8 h, respectively. Patients with a GFR between 10 and 35 ml/min per 1.73 m^2 should be given the standard dose every 12 h.

It can be approximated by a model- and route-independent method that drug accumulates in the body if it is given at intervals of less than 1.4 times the elimination $t_{1/2}$ of serum, when the average amount of drug in the body is considered. It can be seen from the results shown in Table 3 that 1.4 times the $t_{1/2}$ of amoxicillin for groups 1 through 4 is 2.73, 3.16, 6.41, and 14.17 h, respectively, indicating that excessive accumulation of amoxicillin should not occur at the dosage intervals recommended on the basis of the pharmacokinetics for clavulanic acid.

No definite dosage recommendation for patients on hemodialysis (GFR, <10 ml/min per 1.73 m^2) can be made on the basis of our results, because the effective loss of drug into the dialysate was not measured. Studies to assess the effective loss into the dialysate are in progress.

When clavulanic acid and amoxicillin are prescribed for treating bacteriuria, inhibitory concentrations of the two agents were measurable after a standard dose for 12 and 24 h in patients with a GFR above and below 35 ml/min per 1.73 m^2, respectively.

In summary, in spite of the more rapid elimination of clavulanic acid compared with that of amoxicillin in patients with renal failure, concentrations of clavulanic acid in serum and urine are in excess of those in patients with normal renal function. This ensures that effective concentrations of clavulanic acid are maintained in patients with renal failure

when amoxicillin-clavulanic acid is administered less frequently as recommended.

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