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Pharmacokinetics of Amoxycillin and Ampicillin in Patients with Renal Failure

Optymalne dawkowanie amoksycyliny i ampicyliny w zależności od stopnia niewydolności nerek

Оптимальное дозирование амоксициллина и ампициллина у больных в разные периоды почечной недостаточности

Disturbance of renal function is connected with the change of pharmacokinetics of used drugs. In many studies a significant impairment of distribution, biotransformation, binding of drugs to plasma protein and accumulation of toxic metabolites has been observed (7). Renal failure can increase sensitivity to administered drugs and on the other hand, administered drugs can aggravate renal disease and intensification of renal failure.

With regard to a very complicated mechanism of reciprocal activity between renal failure and applied drugs, it seems possible that mathematical formulas for the calculation of administered doses should be applied only exceptionally in renal failure (7). This examination should be specially made with drugs that have urinary excretion as a major pathway of elimination. Semisyntetic penicillines such as amoxycillin and ampicillin produced by Tarchomin "Polfa" belong to these drugs.

MATERIALS AND METHODS

Patients divided into four groups approximately at the same age and sex were tested (Table 1). Group I comprised patients with normal renal function, group II

with creatinine clearance (C_{cr}) ranging from 70 to 20 ml/min, group III patients with C_{cr} from 20 to 10 ml/min and group IV patients with C_{cr} less than 10 ml/min. The cause of renal failure were chronic isolated renal diseases, exclusively. Diet was adequate to the degree of renal failure.

Amoxycillin in tabl. à 250 mg No of series 141277 and Ampicillin in tabl. à 500 mg (different series) were manufactured by Tarchomin "Polfa".

Table 1. Groups of examined patients

Group No	Age from-to	Age average	Sex ♀	Sex ♂	Creatinine clearance $\bar{x}$	Creatinine clearance ±SE
I	21–72	38	10	9	117.6	7.8
II	22–74	48	9	10	47.5	6.3
III	25–77	46	9	6	14.1	1.1
IV	24–71	53	8	8	4.4	0.8

Pharmacokinetic studies were begun at 8 a.m. After blood samples were taken from them, the patients were administered one tablet of amoxycillin or ampicillin.

Then the blood samples were taken after 30, 45 and 60 min and after 2, 3, 4, 6, 8, 12 hr. Until 11 hr a.m. patients had no meals.

Simultanously, every 3 hours urine was collected in which concentration of drugs was estimated. Pharmacokinetics of both drugs in the same patients were tested. Interval between amoxycillin estimation was 3 days.

The calculation of pharmacokinetic parameters was based on one compartment pharmacokinetic model. Maximal drug concentration (C_{max}), time of appearance of C_{max} from the moment of oral administration of drug (t_{max}) and constant of elimination (k) were measurred in each patient according to the following formula:

$$k = \frac{\Sigma t_i \ln C_i - 1/n\,(\Sigma t_i)\,(\Sigma \ln C_i)}{\Sigma t2/1 - 1/n\,(\Sigma t_i)^2}$$

t_i — the time from taking blood to the moment of drug administration,
C_i — drug concentration in blood in time t_i.
Half life time ($t_{1/2}$) was calculated for separate groups of patients

$$t_{1/2} = \frac{-0.693}{k}$$

The dose of a drug for patients with renal failure (D_{nn}) was calculated by steady — state interval time as follows:

$$D_{nn} = D_{nor} \frac{k_{nn}}{k_{nor}}$$

D_{nor} — the dose for healthy persons,
k_{nor} — elimination rate constant of group I,

k_{nn} — constant of elimination of tested group.

The interval between doses, to obtain steady — state drug concentration of the patients with renal failure (T_{nn}), was calculated as follows:

$$T_{nn}=T_{nor}\frac{k_{nor}}{k_{nn}}$$

T_{nor} — normal interval between doses (6 hours).

The proper way of dose application was checked. For that purpose, the previously calculated dose of drug was administered orally to 5 patients from each group for two days. On the next day the blood was taken for the measurement of drug concentration during the time ($t_{c\,max}$) and $t_{c\,mio}$. As previously, examinations were conducted preserving a 3-day interval between administration of amoxycillin and ampicillin.

The determination of blood and urine concentration of amoxycillin and ampicillin was carried out by a spectrofotometric method (Angelucci and Baldieri 1).

Table 2. Some calculations of basic pharmacokinetics parameters in four groups of patients and foreseen optimal dosage of ampicillin and amoxycillin

Group		Ampicillin				Amoxycillin			
		I	II	III	IV	I	II	III	IV
$t_{C_{max}}$	$\bar{x}$	1.417	2.050	3.075	2.844	1.714	2.861	2.880	2.875
	SD	0.750	1.337	1.630	1.407	0.951	1.867	1.810	1.458
C_{max}	$\bar{x}$	12.167	9.790	12.410	10.250	11.07	12.667	11.690	12.563
	SD	7.782	4.148	4.290	4.583	4.495	5.250	5.210	5.506
k		-0.399	-0.225	-0.157	-0.096	-0.365	-0.297	-0.202	-0.088
$t_{1/2}$		1.736	3.086	4.411	7.220	1.900	2.331	3.437	7.848
N		9	10	10	8	7	9	8	8
D_{nor} /mg/hr/		500/6				250/6			
D_{nn} /mg/hr/			281/6	197/6	120/6		203/6	138/6	60/6
T_{nn} in hr for D_{nor}			10.6	15.25	24.94		7.37	10.84	24.89
$TD_{nn\ corr.}$ /mg/hr/			500/8	500/12	250/12		250/8	250/12	125/12

t_{Cmax} — time of appearance maximal concentration (in hours);

C_{max} — maximal concentration in μg/ml;

k — elimination constant;

D_{nor} — dosage for healthy subjects;

D_{nn} — dosage for patients with renal failure every 6 hours;

T_{nn} — time interval for patients with renal failure with administration D_{nor};

$TD_{nn\ corr.}$ — corrected interval time with modification dosage for patients with renal failure.

RESULTS

We have tested pharmacokinetics of ampicillin and amoxycillin in healthy patients and in patients with different degrees of renal failure to elaborate precise doses.

As has been shown, (Table 2) the constant rates of elimination of amoxycillin and ampicillin were similar in different groups of tested patients. The elimination rate constants were decreased during development of renal failure.

The 24 hr excretion of amoxycillin in urine (calculated in % of given dose) was nearly two times higher than that of ampicillin (Fig. 1). When the renal function was decreased, the 24 hr excretion of amoxycillin in urine was decreased as follows: for group I — 49%, group II — 29%, group III — 26%, group IV — 14%.

Ampicillin excretion was found for group I — 28%, group II — 15%, group III — 11%, group IV — 9% (Fig. 1).

The obtained results allowed us to define the following scheme of

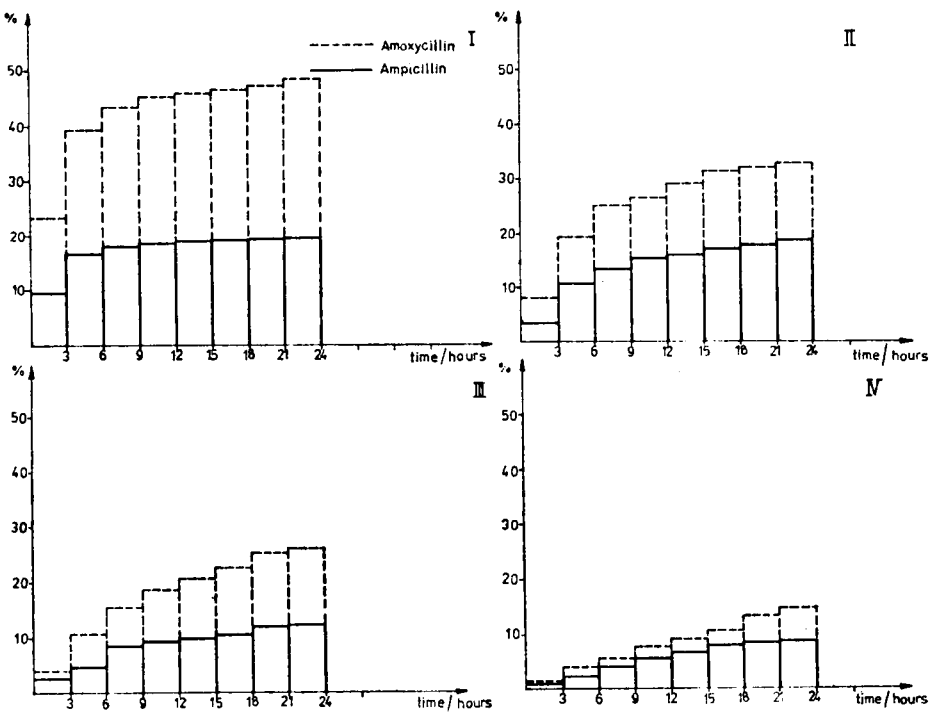

Fig. 1. 24 hours excretion of amoxycillin and ampicillin in urine (in % of administered doses); I — healthy subjects, II — patients with creatinine clearaces from 70 to 20 ml/min, III — patients with creatinine clearances from 20 to 10 ml/min, IV — patients with creatinine clearances below 10 ml/min

doses for different groups of the examined patients with different degree of renal failure ($T_{Dnn\ corr}$ — Table 2).

In all cass tested the constant therapeutic concentration of examined drugs in the blood was determined. In group I the concentration of amoxycillin (μg/ml) varied from 2.5 to 12.5, in group II from 3 to 19, in group III from 3.0 to 16.5, in group IV from 6.5 to 23.5 (Fig. 2). Similar blood concentration of ampicillin ranged from to 12.5 in group I, from 3.5 to 23.5 in group II, from 4 to 15.5 in group III, from 3 to 15.5 in group IV (Fig. 2).

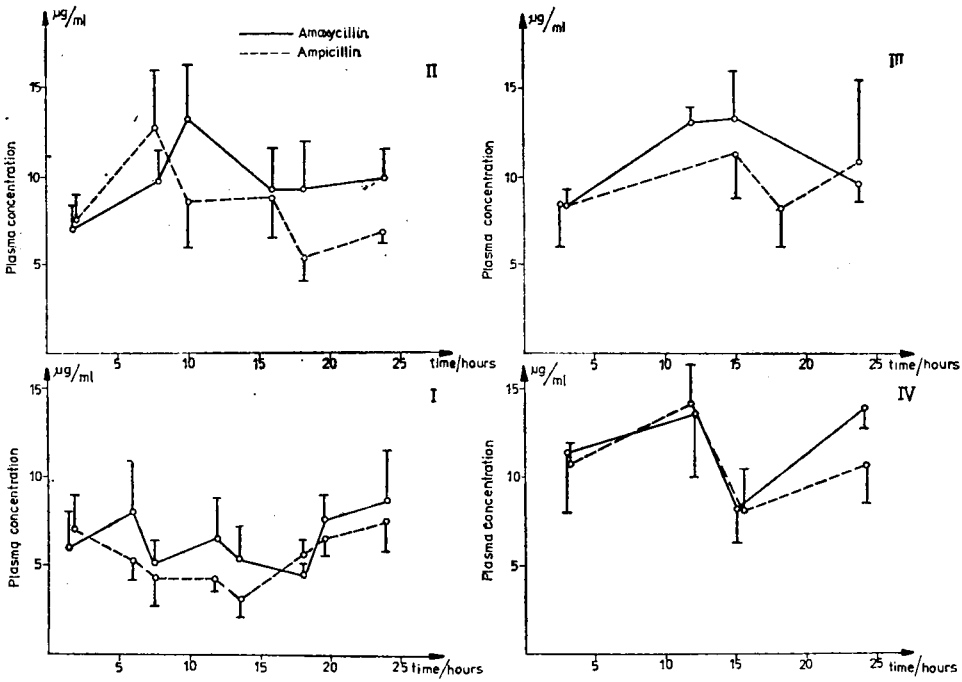

Fig. 2. Curves of plasma in amoxycillin and ampicillin concentrations in the second day of administration in patients with different creatinine clearances; I — healthy subjects, II — patients with creatinine clearances from 70 to 20 ml/min, III — patients with creatinine clearances from 20 to 10 ml/min, IV — patients with creatinine clearances below 10 ml/min; each point is mean ±SE, $n=5$

DISCUSSION

Antimicrobial properties of newly synthetized semisyntethic penicillins have been described by Sutherland and Rolinson in 1970 (6). Amoxycillin, similar to other penicillins, is stable in acetic solutions and it is well resorbed by the digestion tract after oral administration (2).

The obtained results confirmed a good resorption of amoxycyllin by the digestion tract. When amoxycyllin was orally administered after a similar interval in a dose two times less than that of ampicillin, a therapeutic blood concentration was found. This finding suggests a better resorption of the former drug. The resorption of the examined drugs is influenced by food intake. M i k i (3) observed a less effective resorption of ampicillin after meals. Amoxycillin resorption also decreased after food intake but to a considerably lesser extent (3, 8).

During our pharmacokinetic investigations, the patients were given drugs before meals, the influence of food intake on the resorption of drugs having been thus eliminated. However, a chronic administration of drugs does not alow us to eliminate this factor as the patients were on an *ad libitum* diet.

It seems that the food intake influences the drug concentration in the blood whereby the time intervals for the maximal and minimal concentrations differ from the expected values. Apart from the food intake, the drug concentration depends on individual variety because the patients took drugs before meals and yet the levels of the drugs differed remarkably.

Despite individual differences in drug concentrations in the blood, both the examined antibiotics, when administered in suggested doses, rapidly reached therapeutic levels, which were constant during chronic treatment. In all patients higher than minimal effective blood levels of the drugs tested were found, in healthy patients only slightly exceeding minimal effective blood concentrations (4).

The results have shown that amoxycillin was eliminated by urine 50% of the administered dose in healthy patients, ampicillin being eliminated in about 25%. A similar excretion of amoxycillin and ampicillin has been shown by other authors (2, 5). Our investigations give evidence that when the renal function deteriorates, a gradual decrease of the quantity of drugs eliminated with urine is observed. Moreover, the results tend to suggest that during the advanced renal failure, the excretion of amoxycillin and ampicillin into urine was much smaller. It confirms the necessity to conduct precise investigations of pharmacokinetics of the drugs in patients with different degrees of renal failure.

Conclusions

1. Amoxycillin is absorbed by the digestion tract two times better than ampicillin.

2. The elimination rate of the drugs tested decreases gradually with the worsening in renal function.

3. The quantity of examinated drugs eliminated with urine decreases with the worsening in renal function and it probably depends on the lesser absorption, enhanced metabolism, or increased elimination by the digestion tract.

4. The necessary reduction of the dose ranges of amoxycillin and ampicillin is not directly proportional to the clearance of creatinin in patients with renal failure.

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STRESZCZENIE

Na podstawie badań farmakokinetyki po doustnym podaniu 500 mg ampicyliny i 250 mg amoksycyliny u osób z normalną funkcją nerek oraz u chorych z różnym stopniem niewydolności nerek obliczono prawidłowe dawkowanie leków, pozwalające na osiągnięcie ich poziomu terapeutycznego. Stwierdzono, że u chorych z klirensem kreatyniny między 70 a 20 ml/min. dawka amoksycyliny winna wynosić 250 mg co 8 godz., u chorych z klirensem kreatyniny od 20 do 10 ml/min. — 250 mg

co 12 godz., a dla chorych nie leczonych dializami z klirensem kreatyniny mniejszym od 10 ml/min. — 125 mg co 12 godz. Dawki ampicyliny winny być dwukrotnie większe. Prawidłowość proponowanych dawek potwierdzono stosując je u chorych z określoną funkcją nerek wykazując stałe utrzymywanie się stężeń przekraczających minimalny poziom działający, a tylko nieznacznie przekraczających stężenia stwierdzane u ludzi z normalną czynnością nerek.

РЕЗЮМЕ

Фармакокинетику ампициллина перорально применяемого в дозе 500 мл и амоксициллина в дозе 250 мг исследовано у лиц с правильной функцией почек и у больных в разных периодах почечной недостаточности. Вычислено правильное дозирование медикаментов, которое способствовало достижению мерапевтического уровня. В группе больных с клиренсом креоминина (C_{Cr}) между 70—20 мл/мин правильная доза амоксициллина должна выносить 250 мг/8 часов, у больных с C_{Cr} между 20—10 мл/мин — 250 мг/12 часов, для больных с C_{Cr} ниже 10 мл/мин — 125 мг/12 часов. Дозы ампициллина должны применятся в два раза больше.