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Pharmacokinetic characteristics of piperacillin/tazobactam

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Abstract. Piperacillin/tazobactam is a new combination of a broad-spectrum penicillin and a beta-lactamase inhibitor. In studies in healthy volunteers, the pharmacokinetics of piperacillin combined with tazobactam were similar to those of piperacillin alone. In contrast, tazobactam administered with piperacillin achieved higher plasma concentrations and had a longer half-life than tazobactam administered alone. Intravenous infusion of 4.0 g piperacillin with 0.5 g tazobactam over 5 min resulted in mean maximum plasma concentrations of 380 μg piperacillin/ml and 35.3 μg tazobactam/ml; half-lives were 1.14 h for piperacillin and 0.92 h for tazobactam. Within 30 min of infusion, piperacillin/tazobactam achieves 16–85% of plasma concentrations in skin, muscle, lung, gallbladder, and intestinal mucosa. Plasma and tissue levels remain above the MIC_{90}s of major pathogens for 2 h post administration. These findings show that piperacillin/tazobactam is a truly synergistic combination which can be expected to be effective in treating a wide variety of infections in the clinical setting.

Key words: Piperacillin – Beta-lactamases – Pharmacokinetics

The combination of the new beta-lactamase inhibitor tazobactam with the well known beta-lactam antibiotic piperacillin has broadened the antibiotic potential of piperacillin to include beta-lactamase-producing strains. The effectiveness of this new combination has been demonstrated in in vitro investigations [1–3] and in animal models of infection [4] and has been confirmed in clinical trials [5]. The purpose of this review is to summarize the pharmacokinetic properties of piperacillin and tazobactam when administered individually and in combination [6]. Of particular interest is the effect of combining these agents on the pharmacokinetic behaviour of each agent individually.

The pharmacokinetics of piperacillin and tazobactam in healthy subjects

During the clinical development of the piperacillin/tazobactam combination, the pharmacokinetic profiles of piperacillin alone, tazobactam alone, and several combinations of piperacillin/tazobactam were investigated. In most of the studies, the compounds were administered intravenously by infusion pump over intervals of 5 or 30 min.

In all studies, drug levels were assessed by validated HPLC procedures [6, 7]. Pharmacokinetic variables (elimination half-life, total clearance, renal clearance, non-renal clearance, apparent volume of distribution at steady-state, and fraction of dose excreted into urine) were determined with standard model-independent methods. The areas under the curves (AUCs) were calculated using the observed concentrations and applying, in most studies, the linear trapezoidal rule in the ascending phase and the log trapezoidal rule in the descending phase. The half-life was determined from the terminal log linear part of the log plasma concentration versus time curve by least squares regression. The peak plasma concentration was determined as the concentration at the end of intravenous infusion.

Piperacillin has been shown previously to be similar to other beta-lactam antibiotics in that its kinetics are characterized by very high maximum plasma concentrations, small volumes of distribution, short half-lives, and a rapid decay in plasma concentrations [8–12]. During the clinical development of piperacillin/tazobactam, the pharmacokinetics of piperacillin as a single agent were further investigated following intravenous infusions of 3.0, and 4.0 g in healthy volunteers (Table 1). When piperacillin/tazobactam was given in a 5 min infusion, the mean maximum piperacillin concentrations were

Dedicated to Peter Nickel, PhD., Professor and Chairman of the Department of Pharmaceutical Chemistry at the University of Bonn on the occasion of his 60th birthday

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Table 1. Pharmacokinetics of piperacillin in healthy volunteers after administration of piperacillin alone and in combination with tazobactam. Values shown are mean values; coefficients of variation are presented in parentheses [13, 31]

Dose Pip/Taz (g/g)	No. of evaluable subjects	Route	C_{max} (μg/ml)	$AUC_{0\text{-}inf}$ (μg·h/ml)	CL_T (ml/min)	V_{ss} (l)	$T_{1/2}$ (h)	Ae %	CL_R (ml/min)	CL_{NR} (ml/min)
4/0.5	6	Inf-30 min	277 (14)	278 (9)	242 (8)	12.3 (7)	0.83 (14)	46.1 (19)	109 (22)	133 (20)
4/0	6	Inf-30 min	284 (15)	286 (18)	240 (17)	11.9 (12)	0.87 (9)	49.0 (7)	116 (15)	124 (20)
3/0	6	Inf-30 min	251 (16)	258 (16)	198 (16)	14.0 (17)	0.82 (10)	60.5 (9)	121 (22)	77 (14)
2/0.25*	8	Inf-5 min	178 (23)[a]	121 (12)	279 (13)	18.8 (18)	1.27 (21)	48.8 (13)	137 (19)	141 (17)
3/0.375	7	Inf-5 min	336 (39)[a]	230 (10)	219 (10)	14.9 (20)	1.04 (14)	51.7 (23)	113 (21)	106 (28)
4/0.5	6	Inf-5 min	380 (27)[a]	294 (11)	229 (8)	15.8 (16)	1.14 (20)	54.6 (14)	125 (16)	104 (19)

[a] Estimated concentration at 5-minutes; C_{max} = maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the concentration-time curve extrapolated to infinity; CL_T = total clearance; V_{ss} = apparent volume of distribution at steady state; $T_{1/2}$ = elimination half-life; Ae % = fraction of dose excreted into urine; CL_R = renal clearance; CL_{NR} = non-renal clearance

* There are no data on 2 g or piperacillin I.V. alone; however, there is no effect of tazobactam on piperacillin values

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178 μg/ml after a 2.0 g dose and 380 μg/ml after a 4.0 g dose. When piperacillin was given alone as a 30 min infusion, the mean maximum plasma level after a 4.0 g dose was 284 μg/ml, about 75% of the value recorded when the same dose was given in a 5 min infusion [13]. Following intravenous infusion of piperacillin/tazobactam, the volumes of distribution were 18.8 l after a dose of 2 g and 15.8 l after a dose of 4 g; thus, there was a slight tendency for volume of distribution at steady state to decrease with dose. The total clearance also tended to decrease with dose. The renal clearance exceeded the creatinine clearance at a dose of 2 g and also showed a slight tendency to decrease with dose. The renal excretion ranged from 46.1 – 54.6%. The half-life of piperacillin was not significantly altered with increasing dose in these studies.

The pharmacokinetic characteristics of the new beta-lactamase inhibitor tazobactam have been studied over the dose range of 0.1 – 1.0 g in healthy volunteers [14] and found to be typical of those for a beta-lactam. As shown in Table 2, the maximum plasma concentrations attained at the end of infusion were roughly proportional to the dose administered. Thus, the blood concentrations attained following a dose of 0.1 g of tazobactam is somewhat less than one fifth of the 0.5 g dose. As the dose was increased, total clearance decreased and, as a consequence, the AUC rose more than proportionally to the dose administered. The volumes of distribution at steady state for tazobactam were 12.8 l following a dose of 0.1 g and 15.8 l following a dose of 1.0 g, reflecting an increase of 20%. The amount of tazobactam excreted unchanged by the kidney was 60.3% following a dose of 0.1 g and 77.0% when the dose was increased to 1.0 g. Renal clearance remained essentially unchanged over the dose range studied, whereas non-renal clearance decreased from 161 ml/min following the 0.1 g dose to 71 ml/min after a dose of 1.0 g. It should be noted that this result may have been confounded by low plasma concentrations of tazobactam following the 0.1 g and 0.25 g doses that were very close to the detection limit. The calculation of half-life may also have been confounded by these low levels

Table 2. Pharmacokinetics of tazobactam in healthy volunteers after administration of tazobactam alone and in combination with piperacillin. Values shown are mean values; coefficients of variation are presented in parentheses [13, 14, 31]

Dose Pip/Taz (g/g)	No. of evaluable subjects	Route	C_{max} (μg/ml)	$AUC_{0\text{-}inf}$ (μg·h/ml)	CL_T (ml/min)	V_{ss} (l)	$T_{1/2}$ (h)	Ae %	CL_R (ml/min)	CL_{NR} (ml/min)
0/0.1	4	Inf-30 min	5.5 (25)	4.1 (22)	418 (22)	12.8 (17)	0.35 (18)	60.3 (42)	257 (53)	161 (64)
0/0.25	3	Inf-30 min	14.0 (23)	11.7 (12)	358 (11)	13.1 (8)	0.45 (7)	71.0 (7)	253 (80)	105 (26)
0/0.5*	4	Inf-30 min	23.5 (15)	20.8 (20)	415 (24)	14.6 (12)	0.44 (17)	70.9 (5)	297 (29)	118 (10)
0/0.75	4	Inf-30 min	45.2 (13)	39.1 (11)	322 (11)	14.0 (19)	0.59 (34)	69.1 (4)	223 (14)	99 (8)
0/1.0	3	Inf-30 min	51.0 (6)	53.5 (29)	327 (26)	15.8 (11)	0.63 (32)	77.0 (9)	257 (33)	71 (9)
0/0.5	6	Inf-30 min	27.1 (9)	23.5 (8)	355 (7)	15.1 (12)	0.67 (17)	75.8 (12)	268 (19)	87.0 (39)
4/0.5	6	Inf-30 min	34.4 (6)	41.4 (4)	202 (4)	12.6 (7)	0.78 (9)	55.4 (14)	104 (18)	98.0 (20)
2/0.25	8	Inf-5 min	16.2 (24)[a]	12.4 (11)	339 (11)	23.2 (26)	0.88 (31)	65.7 (16)	228 (14)	110 (44)
3/0.375	7	Inf-5 min	28.9 (39)[a]	23.8 (15)	267 (15)	19.0 (23)	0.94 (14)	69.0 (23)	187 (25)	80 (52)
4/0.5	6	Inf-5 min	35.3 (38)[a]	31.7 (13)	270 (12)	19.2 (19)	0.92 (17)	68.2 (14)	188 (23)	82 (25)

[a] Estimated concentration at 5-minutes; C_{max} = maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the concentration-time curve extrapolated to infinity; CL_T = total clearance; V_{ss} = apparent volume of distribution at steady state; $T_{1/2}$ = elimination half-life; Ae % = fraction of dose excreted into urine; CL_R = renal clearance; CL_{NR} = non-renal clearance

* Piperacillin/tazobactam 0/0.5 dose is from two separate studies

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since at the low doses too few data points were available to determine half-life reliability. The half-life increased with dose: following the dose of 0.1 g the half-life was significantly lower than that following the dose of 1.0 g ($p < 0.05$).

The effect of combining piperacillin and tazobactam on the pharmacokinetic behavior of each of these agents has been investigated with piperacillin/tazobactam combinations of 2 g/0.25 g, 3 g/0.375 g, and 4 g/0.5 g. In all studies, when piperacillin and tazobactam were given together in a ratio of 8:1, the pharmacokinetics of piperacillin remained unaffected by tazobactam. In contrast, the pharmacokinetic characteristics of tazobactam were significantly affected by the presence of piperacillin. The plasma concentrations of tazobactam achieved were higher, and the half-life increased from 0.44 h after a dose of 0.5 g of tazobactam alone to 0.78 h after a dose combining 4.0 g piperacillin with 0.5 g tazobactam. As a result, following the combination dose, tazobactam's half-life was very similar to the 0.83 half-life of piperacillin, and the plasma levels of the two compounds administered concurrently parallelled one another.

The reason the pharmacokinetics of tazobactam are affected by coadministration of piperacillin is related to the fact that the predominant pathway of elimination for both tazobactam and piperacillin is renal, accounting for 50–60% of the dose after combined administration. Administration of a single dose of 1000 mg probenecid 1 h before infusion of piperacillin/tazobactam resulted in decreases in the renal clearances of piperacillin and tazobactam of 21% and 25%, respectively [15]. These results indicate that piperacillin and tazobactam both use the same excretion mechanism of tubular secretion in the kidney. Both compounds are also significantly excreted by glomerular filtration or ultrafiltration since they both have a low protein binding making significant amounts of each agent available for ultrafiltration. Because piperacillin and tazobactam are given in an 8:1 ratio, there is competitive inhibition for transport at the renal site in favor of piperacillin. This leads to elevation of the blood levels of tazobactam. Piperacillin and tazobactam are also eliminated to a much lesser extent through hepatic and gastrointestinal routes, but these routes are of little significance from a pharmacokinetic standpoint.

The mean maximum plasma concentration values for piperacillin and tazobactam following administration of several piperacillin/tazobactam combinations are presented in Tables 1 and 2, respectively. As described for piperacillin alone, the duration of infusion significantly affected the maximum plasma concentrations of piperacillin and tazobactam. Mean peak levels of piperacillin at the end of a 5 min infusion of piperacillin/tazobactam were 178 μg/ml after a dose of 2 g/0.25 g, 336 μg/ml after a dose of 3 g/0.375 g, and 380 μg/ml after a dose of 4 g/0.5 g. After a 30 min infusion, mean peak piperacillin levels were 125 μg/ml after a dose of 2 g/0.25 g and 277 μg/ml after a dose of 4 g/0.5 g [13]. Mean peak levels of tazobactam at the end of the 5 min infusion were 16.2 μg/ml after a dose of 2 g/0.25 g, 28.9 μg/ml after a dose of 3 g/0.375 g, and 35.3 μg/ml after a dose of 4 g/0.5 g. After the 30 min infusion, mean peak tazobactam levels were 15.6 μg/ml after a dose of 2 g/0.25 g and 34.4 μg/ml after a dose of 4 g/0.5 g [13]. At the end of the 5 min infusion, the ratio of piperacillin/tazobactam was 11:1, and 3–4 h after the 5 min infusion, the ratio was 7:1. In comparison, at the end of the 30 min infusion, the ratio of piperacillin/tazobactam was 8:1, and 3–4 h after the 30 min infusion, the ratio was 4:1. In all regimes presented here, the plasma concentrations of both piperacillin and tazobactam were maintained well above the MIC_{90}s of major Gram-positive, Gram-negative, and anaerobic pathogens for 2 h post administration [16, 17].

Administration of piperacillin/tazobactam to patients with compromised renal function

Because piperacillin is eliminated primarily through the kidneys, its dosage must be adjusted according to renal function. Creatinine clearance has been shown to predict the renal clearance of tazobactam indicating that its dosage may be adjusted according to renal function in the same manner as adjustments are made for piperacillin in renally compromised patients. The findings of two studies of piperacillin/tazobactam in renally compromised patients are presented in Table 3. The results of the studies, one using piperacillin/tazobactam in an 8:1 ratio (3.0 g piperacillin/0.375 g tazobactam) and the other using the combination in a 4:1 ratio (2.0 g piperacillin/0.5 g tazobactam) were similar [18, 19]. The elevation of maximum plasma concentrations of either compound in renally compromised patients was never more than 50% above the concentrations in normal healthy controls. In patients whose creatinine clearance was less than 20 ml/min, tazobactam's AUC was an average of 4–5 times that in the normal healthy controls, while piperacillin's AUC was, on the average, only 3 fold that of the controls. The renal clearance of both compounds was between 8 and 11 fold less than normal. The nonrenal clearance in patients with creatinine clearance less than 20 ml/min was close to 2 fold less than that in the normal controls, except in piperacillin-treated patients given a dose of 3.0 g/0.375 g. These findings indicate that reduction in creatinine clearance has a greater effect on the total clearance of tazobactam than on that of piperacillin. This is because in the normal healthy individual the renal excretion of unchanged tazobactam is higher than that of piperacillin. Nevertheless, the difference between piperacillin and tazobactam in the changes in total clearance that occur in renally compromised patients are not of sufficient magnitude to warrant adjustment of the dose of tazobactam independent of that of piperacillin. Because the total clearance of tazobactam is more profoundly affected than that of piperacillin in renally compromised patients, the elimination half-life is affected to a greater extent as well.

In patients with normal renal function, the severity and type of infection determines the intervals at which doses of piperacillin/tazobactam are administered (every 4, 6, or 8 h). In renally compromised patients with a creatinine clearance of less than 40 ml/min, the dosage interval must be extended: renally compromised patients

Table 3. Effect of renal failure on the pharmacokinetics of piperacillin and tazobactam. Values shown are mean values; coefficients of variation are presented in parentheses [18, 19, 31]

Dose Pip/Taz (g/g)	No. of evaluable subjects	Creatinine clearance (ml/min)	Compound measured	C_{max} (μg/ml)	$AUC_{0\text{-inf}}$ (μg·h/ml)	CL_T (ml/min)	V_{ss} (l)	$T_{1/2}$ (h)	Ae %	CL_R (ml/min)	CL_{NR} (ml/min)
3/0.375	8	>90	Pip	209 (27)	228 (17)	225 (17)	14.9 (29)	0.95 (20)	74.0 (29)	168 (36)	57 (87)
	8	60–90		228 (25)	323 (17)	159 (18)	13.0 (31)	1.10 (22)	48.8 (31)	76.5 (28)	83 (39)
	9	40–60		274 (28)	417 (32)	134 (41)	12.5 (31)	1.26 (23)	45.5 (24)	57.7 (26)	76 (60)
	13	20–40		248 (26)	462 (23)	114 (25)	12.4 (29)	1.43 (21)	34.0 (35)	37.5 (31)	77 (30)
	12	<20		253 (30)	665 (32)	83 (34)	13.1 (28)	1.92 (40)	21.3 (73)	15.6 (54)	67 (40)
	8	>90	Taz	23.6 (27)	29.0 (14)	219 (14)	15.9 (26)	0.89 (16)	64.5 (26)	148 (33)	71.5 (44)
	8	60–90		27.6 (35)	44.6 (21)	147 (23)	14.7 (38)	1.21 (33)	58.7 (26)	88.7 (34)	58.1 (35)
	9	40–60		30.4 (36)	59.1 (32)	118 (39)	14.4 (37)	1.47 (30)	52.4 (16)	63 (31)	54.8 (54)
	13	20–40		29.4 (29)	84.0 (23)	78.1 (22)	14.0 (29)	2.09 (25)	42.6 (34)	35.5 (38)	42.6 (33)
	12	<20		31.6 (39)	146 (39)	49.5 (45)	15.2 (34)	3.58 (65)	22.9 (52)	12.5 (50)	37.0 (55)
2/0.5	8	>90	Pip	113 (15)	116 (22)	299 (21)	17.5 (19)	1.18 (71)	45.6 (14)	136 (23)	163 (26)
	9	40–89		126 (27)	174 (26)	203 (24)	16.8 (26)	1.31 (45)	38.5 (24)	79.8 (40)	123 (23)
	7	20–39		171 (30)	325 (16)	105 (16)	13.5 (26)	1.84 (20)	24.7 (29)	25.9 (32)	79.1 (22)
	7	<20		168 (25)	340 (25)	104 (30)	14.1 (22)	2.01 (18)	12.2 (56)	12.2 (50)	92.0 (33)
	8	>90	Taz	29.5 (22)	37.8 (32)	238 (27)	16.9 (17)	1.04 (82)	63.7 (11)	155 (29)	82.7 (36)
	9	40–89		30.2 (26)	55.4 (23)	158 (23)	17.9 (24)	1.56 (44)	60.1 (19)	97.4 (34)	60.4 (30)
	7	20–39		40.1 (23)	105 (32)	90 (47)	14.8 (23)	2.22 (50)	45.1 (24)	44.4 (70)	45.6 (30)
	7	<20		38.5 (26)	152 (32)	59.5 (29)	17.1 (21)	3.54 (43)	30.7 (45)	19.2 (55)	40.3 (31)

C_{max} = maximum plasma concentration; $AUC_{0\text{-inf}}$ = area under the concentration-time curve extrapolated to infinity; CL_T = total clearance; V_{ss} = apparent volume of distribution at steady state; $T_{1/2}$ = elimination half-life; Ae % = fraction of dose excreted into urine; CL_R = renal clearance; CL_{NR} = non-renal clearance

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who would be treated every 4 or 6 h if renal function were normal would be treated every 6 or 8 h instead. In patients with comparable infections whose creatinine clearance is less than 20 ml/min, the dosage interval should be extended further to every 8 or 12 h. In patients whose creatinine clearance is less than 20 ml/min who would require treatment with piperacillin/tazobactam every 8 h if renal function were normal, the treatment interval should be increased to 12 h. Piperacillin as a single agent has a well established role in the treatment of patients with renal failure. The dosage regimens described above were derived from studies of the new combination of piperacillin/tazobactam in renally compromised patients and are consistent with the established regimens of piperacillin alone in patients with decreased kidney function.

In patients undergoing kidney dialysis, about one-third of the dose of piperacillin/tazobactam should be replaced to account for the loss of active agents that occurs during hemodialysis. Current data indicate that patients undergoing peritoneal dialysis do not require similar replacement of active drugs since only 6% of the piperacillin dose and 13% of the tazobactam dose are removed during this type of dialysis.

The effects of coadministration of tobramycin or vancomycin on the pharmacokinetics of piperacillin/tazobactam

The degree to which the piperacillin/tazobactam combination interacts with other therapeutic agents is also of clinical interest. The extent of interaction between piperacillin/tazobactam and other agents depends primarily on the degree and the mechanism of renal excretion of the agents coadministered. Compounds primarily eliminated by glomerular filtration are unlikely to affect compounds primarily excreted by tubular secretion. Agents that are eliminated predominantly by the liver or gastrointestinal tract would have no significant effect on the overall pharmacokinetics of an agent excreted by the kidney and vice versa. Although a few exceptions exist, these simple statements on drug-drug interactions hold generally true.

During investigations of the extent of drug interaction, piperacillin/tazobactam has been coadministered with tobramycin, a compound with very low protein binding that is eliminated entirely by glomerular filtration, and vancomycin, which also has low protein binding and is eliminated primarily by glomerular filtration [23]. As Table 4 shows, there were only minor changes in the pharmacokinetic behaviors of tazobactam and piperacillin in these interaction studies. The elimination half-lives of tazobactam and piperacillin were slightly less when piperacillin/tazobactam was coadministered with tobramycin than when administered alone, but the maximum concentrations achieved in plasma and the AUC were essentially the same. The pharmacokinetic characteristics of tobramycin were significantly ($p < 0.05$) altered when tobramycin was coadministered with piperacillin/tazobactam: the renal clearance of tobramycin decreased from 60.7 to 41.4 ml/min and the AUC increased by 12%. These changes, however, are unlikely to significantly affect the clinical antimicrobial activity of tobramycin. The diminished renal elimination of tobramycin may have been caused by a chemical reaction between piperacillin and tobramycin in vitro; the fact that the renal excretion

Table 4. Pharmacokinetics of tazobactam and piperacillin after concomitant administration with tobramycin or vancomycin in nine evaluable subjects. Values shown are mean values; coefficients of variation are presented in parentheses [23, 31]

Dose Pip/Taz (g/g)	Dose of tobramycin[a] or vancomycin[b]	Compound measured	C_{max} (μg/ml)	$AUC_{0\text{-inf}}$ (μg·h/ml)	$T_{1/2}$ (h)
3/0.375	–	Pip	195 (17)	220 (20)	0.89 (13)
		Taz	21.6 (14)	27.6 (18)	0.85 (13)
3/0.375	Tobramycin[a] 1 mg/kg	Pip	203 (18)	224 (20)	0.79 (12)
		Taz	23.1 (12)	28.6 (20)	0.78 (8)
		Tobramycin	7.35 (23)	16.1 (18)	2.52 (16)
–	Tobramycin[a] 1 mg/kg	Tobramycin	7.30 (18)	18.2 (21)	2.41 (12)
3/0.375	–	Pip	176 (14)	197 (14)	0.84 (16)
		Taz	23.2 (6)	28.1 (16)	0.91 (19)
3/0.375	Vancomycin[b] 0.5 g	Pip	169 (8)	210 (11)	0.81 (17)
		Taz	22.2 (11)	29.4 (16)	0.88 (23)
		Vancomycin	23.1 (12)	93.8 (17)	8.32 (27)
–	Vancomycin[b] 0.5 g	Vancomycin	23.6 (8)	92.4 (15)	7.77 (25)

[a] Tobramycin was administered as a 30 minute IV infusion; [b] Vancomycin was administered as a 60-minute IV infusion; C_{max} = maximum plasma concentration; $AUC_{0\text{-inf}}$ = area under the concentration-time curve extrapolated to infinity; $T_{1/2}$ = elimination half-life
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of piperacillin was not affected has yet to be explained. The peak of MIC concentration, which has been found to predict the outcome of aminoglycoside treatment of patients with severe infections [21, 22], was unaltered. Further, the frequency and severity of adverse events associated with tobramycin treatment did not appear to change when tobramycin was coadministered with piperacillin/tazobactam. That there were no clinically significant interactions between these agents leads to speculation that there would be no interaction between the piperacillin/tazobactam combination and gentamicin as well.

The pharmacokinetic effects of coadministration of vancomycin and the piperacillin/tazobactam combination have also been investigated [23]. Following infusion of vancomycin, the total clearance of piperacillin was decreased by 7%, while that of tazobactam was not affected. Although this decrease was statistically significant, it was not large enough to warrant an alteration in dose or dosage regimen. These studies did not reveal any clinically significant alterations in any of the pharmacokinetic variables for vancomycin of piperacillin/tazobactam when these agents were administered together. Coadministration of tobramycin [20] or vancomycin [23] with piperacillin/tazobactam does not likely affect the pharmacokinetics of the individual compounds since vancomycin and tobramycin are eliminated predominantly through glomerular filtration whereas piperacillin and tazobactam are eliminated mostly by tubular secretion.

Tissue penetration of piperacillin/tazobactam

The importance of the levels of therapeutic compounds attained in individual tissues remains a point of controversy. Yet, recent investigations with new compounds such as the macrolides suggest [24, 25] that tissue levels may be more important than previously thought, since the effectiveness of these compounds cannot be explained on the basis of plasma levels alone.

For investigations of the tissue penetration of piperacillin/tazobactam, several studies in patients undergoing abdominal or thoracic surgery, including cholecystectomy and prostate resection [6, 26–28] were conducted. In these studies, patients received piperacillin/tazobactam doses of 4.0 g/0.5 g, 3.0 g/0.375 g, and 2.0 g/0.5 g. Additionally, the penetration of both compounds into blister fluid was investigated after administration of the 4.0 g/0.5 g combination [29]. Within 30 min of infusion, piperacillin/tazobactam achieved from 16–85% of plasma concentrations in the skin, muscle, lung, gallbladder, and intestinal mucosa; these levels significantly exceed the MIC_{90} of most bacterial species [30]. The concentration time courses and penetration ratios for piperacillin and tazobactam were generally similar (Fig. 1). Differences in penetration into tissues and organs may be partly explained by physiological properties such as water content and blood perfusion or active processes by which the drugs are taken up by cells. Also, differences in the molecular weights or molecular sizes of piperacillin and tazobactam may be responsible for any slight differences in tissue distribution between the two agents. Tazobactam and piperacillin are hydrophilic; therefore, in general, they are distributed well, with the exception of distribution into tissues that have a low water content, such as fat.

The highest tissue concentrations of piperacillin and tazobactam were found in the gastrointestinal tract, except for the omentum (Fig. 2). After 60–90 min, almost 70 μg/g of piperacillin was detected in the distal intestinal mucosa. At 60–90 min after initiation of infusion, the concentration of tazobactam in the distal mucosa of the intestine was above 20 μg/g. Concentrations of both piperacillin and tazobactam in the omentum were below 10% of plasma concentrations.

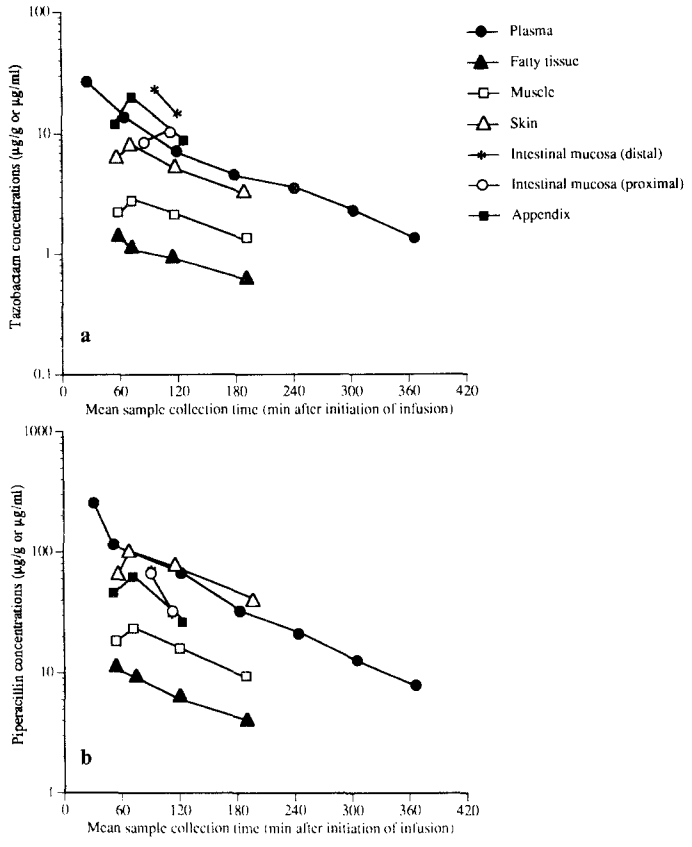

Fig. 1 a, b. Mean tazobactam (**a**) and piperacillin (**b**) concentrations in plasma and tissues of colorectal surgery patients after an intravenous infusion (4 g of piperacillin, 0.5 g of tazobactam) [6]. Reprinted with permission from the American Society of Microbiology

Tazobactam and piperacillin penetrated well into skin, where both compounds reached between 50% and 111% of plasma concentrations. Following administration of piperacillin/tazobactam as the 4.0 g/0.5 g combination, the mean peak concentration of piperacillin was 94.2 ± 27.8 µg/g and that of tazobactam was 7.73 ± 2.39 µg/g. The mean drug concentrations in muscle

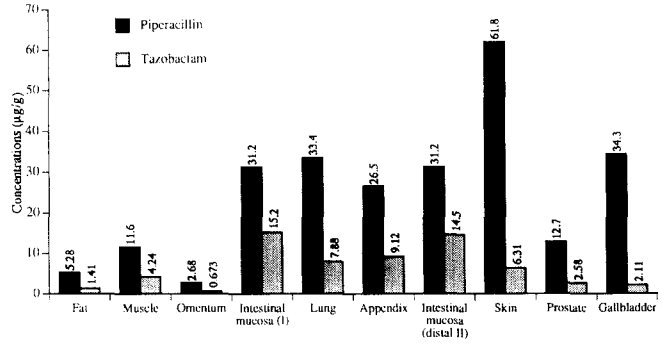

Fig. 2. Mean tissue concentrations of piperacillin and tazobactam in selected tissues 90–150 min after administration of piperacillin/tazobactam in doses of 2 g/0.5 g (data for fat, muscle, omentum, intestinal mucosa [I], lung, and prostate), 4 g/0.5 g (data for appendix, intestinal mucosa [distal, II], and skin), and 3 g/0.375 g (data for gallbladder) [6,31]. Mean values (fat: $n = 16$, muscle: $n = 11$, omentum: $n = 7$, intestinal mucosa (I), $n = 10$; lung: $n = 6$; appendix: $n = 9$; intestinal mucosa (distal II): $n = 10$; skin: $n = 12$; prostate: $n = 7$; gallbladder: $n = 8$). (Reprinted with permission from the Journal of Antimicrobial Chemotherapy)

at least 120 min after the start of infusion of piperacillin/tazobactam as the 4.0 g/0.5 g or 2.0 g/0.5 g combination was above 10 µg/g for piperacillin and above 2 µg/g for tazobactam. Consistent with findings in other beta-lactam antibacterials, the penetration of piperacillin and tazobactam into fatty tissue was low; concentrations of both drugs in fatty tissues were only about 10% for piperacillin and 14% for tazobactam plasma concentrations.

Both piperacillin and tazobactam penetrated well into the lung. The levels of piperacillin in lung tissue between 90 and 150 min were similar to those in the plasma; the mean lung tissue: plasma ratio for piperacillin was 0.918 ± 0.163. Maximum levels of piperacillin and tazobactam were achieved about 30 min following the end of infusion of 2.0 g/0.5 g piperacillin/tazobactam and were as high as 40.8 ± 16.6 µg/g and 8.63 ± 3.65 µg/g, respectively. The mean lung tissue: plasma ratio for piperacillin was 0.775.

Drug concentrations in the gallbladder after administration of the 3.0 g/0.375 g combination were particularly high for piperacillin (34.3 ± 19.5 µg/g) but were much lower for tazobactam (2.11 ± 1.12 µg/g). In bile, piperacillin concentrations were between 220 and 1045 µg/ml, and tazobactam concentrations were between 1.33 and 42.9 µg/ml.

Investigations of the penetration into prostatic tissue and prostatic fluid were performed with the 2.0 g/0.5 g combination of piperacillin/tazobactam. The highest concentrations in prostatic tissue were reached within one hour after the start of infusion and were 17.9 ± 10.6 µg/g for piperacillin and 5.50 ± 2.46 µg/g for tazobactam. In prostatic fluid, concentrations up to 7.24 µg/ml for piperacillin and 2.92 µg/ml for tazobactam were measured.

The penetration into blister fluid was studied after the administration of 0.5 g tazobactam either alone or in combination with 4 g piperacillin. The AUC in the blister fluid was 46.7–67.7% for tazobactum and 49.6% for piperacillin of the plasma AUC [29].

Conclusions

The data reported here indicate that the pharmacokinetic behavior of the well established beta-lactam antibiotic piperacillin when given in combination with the new beta-lactamase agent tazobactam is similar to the pharmacokinetic behavior of piperacillin alone. The pharmacokinetics of tazobactam alone are typical of those of a beta-lactam. Administration of tazobactam in combination with piperacillin leads to increases in its half-life and maximum plasma concentration. As a result the plasma concentration-time curves of the two agents parallel one another, making this new combination a particularly well tailored, truly synergistic combination of antibacterial agents. Tissue penetration of both agents are generally excellent; levels in the skin, muscle, lung, gallbladder, and intestinal mucosa range from 16% to 85% of plasma levels and exceed the MIC_{90} of most bacterial species. The pharmacokinetic profile of the new antibacterial combination piperacillin/tazobactam therefore suggests that this agent will perform well in clinical use.

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