Administration of ticarcillin in combination with clavulanic acid intravenously and intrauterinely to clinically normal oestrous mares

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Van Camp, S. D., Papich, M. G., Whitacre, M. D. Administration of ticarcillin in combination with clavulanic acid intravenously and intrauterinely to clinically normal oestrous mares. *J. vet. Pharmacol. Therap.* **23,** 373–378.

Ticarcillin and clavulanic acid (potassium clavulanate) were administered to normal oestrous mares intravenously (i.v.) at a dose of 50 and 1.67 mg/kg for ticarcillin and clavulanate, respectively. In a crossover design, the same drugs were administered intrauterine (i.u.) at a dose of 12.4 and 0.4 mg/kg for ticarcillin and clavulanate, respectively. The i.u. dose was administered in 100 mL of saline solution. Endometrial tissue biopsies and plasma samples were collected after drug administration for the determination of ticarcillin and clavulanate concentrations by high-pressure liquid chromatography and pharmacokinetic calculations. After i.u. administration both drugs were poorly absorbed into the plasma. The ticarcillin half-life from tissue and plasma was short after i.v. administration. Although concentrations in tissue were higher after i.u. administration than i.v., concentrations of ticarcillin declined rapidly, which would necessitate frequent treatment in order to maintain drug concentrations above the minimum inhibitory concentrations (*MIC*) throughout the treatment period. Clavulanate concentrations in tissue were either low or persisted for only a short time after administration via either route. It appears that addition of clavulanate to the formulation for treatment of i.u. infections in mares is of questionable value based on these concentrations.

(Paper received 15 February 2000; accepted for publication 8 September 2000)

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INTRODUCTION

Ticarcillin, a semi-synthetic penicillin with a broad spectrum of anti-microbial activity, has been used to treat endometritis in mares. It is recommended as a drug of choice for the treatment of *Pseudomonas* sp., especially *Psuedomonas aeruginosa*, as it is up to four times more active than the anti-*Pseudomonas* antibiotic carbenicillin (Sutherland *et al.*, 1970; Mandell & Sande, 1990). Like most penicillins, ticarcillin has a β-lactam ring which is susceptible to β-lactamases produced by a number of bacteria, including Enterobacteriaceae and gram-positive organisms such as *Streptococcus* and *Staphylococcus* (Mandell & Sande, 1990; Rice & Bonomo, 2000).

In an effort to counteract β-lactamases, ticarcillin and amoxicillin have been combined with clavulanic acid in the form of potassium clavulanate. Clavulanic acid is structurally similar to penicillins and competitively binds to the same sites on the β-lactamase molecules as the antibiotics, thus inhibiting the β-lactamase enzyme by forming an irreversible inactive complex of the enzyme and clavulanate (Neu & Fu, 1978; Gould & Wise, 1988). Ninety per cent of equine origin *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* sp. isolates were sensitive *in vitro* to ticarcillin when combined with clavulanic acid (Sparks *et al.*, 1988). Clavulanic acid does not overcome resistance to ticarcillin by non-β-lactamase-producing bacteria. Ticarcillin is active against *Pseudomonas* but clavu-lanic acid does not inhibit the class-C β-lactamases (Ambler classification system) (Rice & Bonomo, 2000) produced by this organism. Therefore, the addition of clavulanic acid to ticarcillin is not expected to increase the effectiveness of ticarcillin against *P. aeruginosa* (Fuchs *et al.*, 1984; Kucers & Bennett, 1987).

The pharmacokinetics of systemic and intrauterine (i.u.) ticarcillin and systemic ticarcillin in combination with clavulanic acid have been described in the mare (Lock, 1982; Threlfall & Keefe, 1983; Sweeney *et al.*, 1984; Spensely *et al.*, 1986; Sweeney *et al.*, 1988a; Leblanc *et al.*, 1989). However,

this study examined the pharmacokinetics and endometrial concentrations of ticarcillin and clavulanic acid when given as a single intravenous (i.v.) bolus or an i.u. infusion for the purpose of assessing optimal treatment regimens. Specifically, this study examined the pharmacokinetics and endometrial tissue concentrations of the commercially available 30:1 combination of ticarcillin and clavulanic acid (Timentin®), after i.v. or i.u. administration to the mare.

MATERIALS AND METHODS

Five clinically normal (Kenney-Doig endometrial biopsy I) (Kenney & Doig, 1989) oestrual mares of various breeds, body weight 410–602 kg and aged 4–8 years were used in this study. The research protocol of animal use and care was approved by North Carolina State University's Institutional Animal Use and Care Committee (IACUC # 90-085). Mares were randomly assigned to either the i.v. or i.u. protocol for the initial trial. Eighteen days minimum (range 18–35) elapsed before the mares were retreated via the alternate protocol after being re-biopsied to reconfirm their endometrial status. In the i.u. protocol, 6 g of ticarcillin combined with 0.2 g of clavulanic acid (30:1 ratio) was dissolved in 100 mL of saline and instilled into the uterus with a plastic syringe and infusion pipette. For intrauterine (i.u.) treatment, the average doses were 12.41 mg/kg of ticarcillin and 0.41 mg/kg of clavulanate. The i.v. protocol consisted of 50 mg/kg of ticarcillin and 1.67 mg/kg of clavulanic acid injected in combination in a 30:1 ratio into the right jugular vein via catheter over a 1-min period. Heparinized vacutainers were used to collect blood prior to treatment and at 5, 15 and 30 min and 1, 3, 5, 8, 12 and 24 h post treatment from the left jugular vein. The blood samples were stored in crushed ice for up to 1.5 h until centrifuged. The plasma was stored at −80 °C until assayed. Endometrial biopsy samples were collected prior to treatment and at 1, 3, 5, 8, 12 and 24 h after treatment. The tissue was weighed and stored on crushed ice for up to 1.5 h then transferred to a −80 °C freezer until assayed. Tissues and plasma were analysed within 50 days of collection; most samples were analysed within 30 days. Penicillins in tissues and plasma are not degraded during storage at this temperature for these intervals (Boison *et al*., 1992). Tissue samples for histopathology were fixed in buffered formalin and prepared by the College of Veterinary Medicine's histopathology laboratory. Histological evaluation was carried out by the author (SVC) using the criteria described by Kenney and Doig (1989).

Plasma and tissue concentration analysis

Plasma and endometrial tissue concentrations of ticarcillin and clavulanate were determined by the previously described high performance liquid chromatography method published by our laboratory (Tyczkowska & Aronson, 1988). This assay had an accuracy of 104% and precision within 3.67% of the mean values. The limit of detection (LOD) defined for the study was 0.05 μg/mL for ticarcillin in plasma and 0.15 μg/g for ticarcillin in tissue. The LOD values for clavulanate were 0.25 μg/mL and 0.5 μg/g for plasma and tissue, respectively. The limit of quantification (LOQ) for the assay was 0.83 and 0.167 μg/mL for clavulanate in plasma and tissue, respectively. All drug concentrations used for pharmacokinetic calculations were greater than LOQ.

Pharmacokinetic analysis

Plasma and tissue concentrations after i.v. and i.u. administration of ticarcillin and clavulanate were plotted on a semi-logarithmic graph. Concentration profiles were analysed by methods described by Gibaldi and Perrier (1982) using compartmental analysis for i.v. administration and non-compartmental methods for the i.u. administration.

Estimates of terms and coefficients in the pharmacokinetic equations were performed with a computer program (Fig. P Version 2.7, Fig. P Software Corporation, Durham, NC, USA; distributed by Biosoft, Ferguson, MO, USA) using the method of least squares. Area under the curve (*AUC*) from time zero to infinity was calculated using the trapezoidal method (Gibaldi & Perrier, 1982). Concentrations from i.v. administration of ticarcillin and clavulanate were analysed using both one- and two-compartment methods to determine the more appropriate model, and pharmacokinetic values were calculated using standard equations (Gibaldi & Perrier, 1982).

RESULTS

Pharmacokinetic analysis was performed for each animal individually and the average values are listed in Tables 1 and 2 and shown in Figs 1 and 2. For some groups of data, there were not sufficient values above the LOQ to calculate meaningful pharmacokinetic values. Tissue concentrations of clavulanate were above the LOD in only a few samples after the i.v. administration. Therefore, calculations would not have been meaningful and were not reported in the tables for this group (indicated by 'nd' in Tables 1 and 2).

After i.u. administration of clavulanate, endometrial tissue concentrations were above the LOQ in only two samples (60 and 180 min) in three out of five mares. In the remaining two mares there were detectable concentrations in only one sample from one mare (60 min), and concentrations were low from 60–1440 min in the remaining mare. These concentrations were not used for pharmacokinetic calculations. There were no detectable plasma concentrations after i.u. administration of 0.41 mg/kg of clavulanate. After i.u. administration of ticarcillin, there were sufficient detectable concentrations in plasma for only two mares to allow calculation of pharmacokinetic values. For these two horses, it was possible to calculate the systemic availability of ticarcillin after i.u. administration by comparing *AUC* from i.v. and i.u. routes. The systemic availability was only 8.2 and 3.4% for these two horses. There were no plasma samples of clavulanate after i.u. administration from which to calculate systemic availability.

Table 1. Comparison of pharmacokinetic parameters for ticarcillin after i.v. administration of ticarcillin (50 mg/kg) and i.u. administration of ticarcillin (12.41 ± 2.07 mg/kg) in horses ($n = 5$); values are means (± SE)

	C_{max} μg/mL (plasma) μg/gm (tissue)	t_{max} min	K_{el} min^{-1}	$t_{1/2}$ min	*MRT*min	*AUC* μg · min/mL	$V_{d(area)}$ L/kg	$V_{d(ss)}$ L/kg	*Cl* mL/kg/min
Plasma concentration after i.v. administration	576.26 ± 70.68	0.00	0.01 ± 0.00	69.3	72.62 ± 0.43	31 080.34 ± 1615.98	0.13 ± 0.01	0.12 ± 0.01	1.631 ± 0.10
Tissue concentration after i.v. administration	75.98 ± 18.21	60.00 ± 0.00	0.01 ± 0.00	69.3	nd	29282.84 ± 4832.88	nd	nd	1.95 ± 0.38
Plasma concentration after i.u. administration	1.21 ± 0.62	72.00 ± 29.39	0.01* ± 0.00	69.3*	nd	381.77 ± 158.31	nd	nd	nd
Tissue concentration after i.u. administration	423.96 ± 119.66	84.00 ± 24.00	0.02 ± 0.00	34.65	nd	46 872.09 ± 14 346.84	nd	nd	nd

nd = not determined because of insufficient data; C_{max} = maximum concentration after administration; t_{max} = time of maximum concentration; K_{el} = elimination rate constant of the terminal slope of concentration–time curve; $t_{1/2}$ = elimination half-life (Harmonic mean); *MRT* = mean residence time; $V_{d(area)}$ = apparent volume of distribution using the area method; $V_{d(ss)}$ = apparent volume of distribution at steady-state; *Cl* = systemic clearance; *AUC* = total area under the concentration vs. time curve from 0 to infinity. *, Elimination rate could be calculated for only two animals; not sufficient data for other animals.

For three of the horses, the plasma concentrations after i.v. administration of ticarcillin were best described with a two-compartment model. For those horses, the distribution-rate constant and distribution half-life were 0.08 min^{-1} and 8.7 min, respectively. A one-compartment model best described plasma concentrations in the other two horses. The value of K_{el}, represents the terminal rate constant for all horses, but represents the elimination rate constant (β) for the data from horses fit to a two-compartment model. The half-life in Table 1 is the harmonic mean for the terminal portion of the curve for all five horses. After i.v. administration of clavulanate, the disposition in one horse was best described by a two-compartment model with a distribution rate and distribution half-life of 0.06 min^{-1} and 11.02 min, respectively. The data for other horses after administration of clavulanate was described by a one-compartment model and listed in Table 2.

DISCUSSION

On the basis of microbiological susceptibility tests, two previous reports recommend that to achieve adequate concentrations in plasma or serum to treat systemic infections, the combination of ticarcillin and clavulanate should be administered i.v. at a dosage of 50 mg/kg ticarcillin and 1.67 mg/kg clavulanate (Sweeney *et al.*, 1988a). This was the basis for the selection of the dose administered i.v. in this study.

The pharmacokinetics of ticarcillin and clavulanate after administration to horses have been reported previously. After i.v. administration to horses, the half-lives of ticarcillin have been reported to be 0.831 h (Spensely *et al.*, 1986; Sweeney *et al.*, 1988a), 0.94 h (Sweeney *et al.*, 1984) and 1.0 h (Sweeney *et al.*, 1988b). In the present study, the terminal half-life of ticarcillin after i.v. administration was slightly longer at 1.15 h. Although we did not examine i.m. pharmacokinetics, the half-life after i.m. administration in other studies was longer owing to the 'flip-flop' effect (Threlfall & Keefe, 1983; Sweeney *et al.*, 1984; 1988a,b).

Ticarcillin had a small apparent volume of distribution in this study ($V_{d(area)}$ 0.13 L/kg), which suggests that its distribution is limited to the extracellular space. Clavulanate had a similarly small $V_{d(area)}$. For drugs that are limited in their distribution to the extracellular space, the tissue fluid concentration should parallel the plasma concentration after a short time for equilibrium (Cars, 1991). The values reported here for $V_{d(area)}$, and systemic clearance (*Cl*) were somewhat lower than what has been reported for ticarcillin after i.v. administration in previous studies (Sweeney *et al.*, 1984; Spensely *et al.*, 1986; Sweeney *et al.*, 1988a,b), but not inconsistent with what one expects for β-lactam antibiotics in animals.

In the study reported here, we calculated a similar plasma elimination rate for ticarcillin for both routes of administration ($t_{1/2}$ 69 min). Likewise, the elimination of ticarcillin was similar for both tissue and plasma when the drug, was administered i.v. This profile in which tissue fluid concentration parallels the plasma concentration is expected for a drug that is limited in its

Table 2. Comparison of pharmacokinetic parameters for clavulanate after i.v. administration of clavulanate 1.67 mg/kg and i.v. administration (n = 5). Values are mean ($\pm$SE).

	C_{max} g/mL µg/mL (plasma) µg/gm (tissue)	t_{max} min	K_{el} min^{-1}	$t_{1/2}$ min	MRTmin	AUC µg · min/mL	$V_{d(area)}$ L/kg	$V_{d(ss)}$ L/kg	Cl mL/kg/min
Plasma concentration after i.v. administration	14.23 ± 1.22	0.00	0.03 ± 0.00	23.1	75.56 ± 16.06	449.57 ± 63.98	0.19 ± 0.05	0.18 ± 0.03	4.05 ± 0.64
Tissue concentration after i.v. administration[†]	0.23 ± 0.16	72.00 ± 58.17	nd	nd	nd	nd	nd	nd	nd
Tissue concentration after i.u. administration	8.67 ± 2.71	84.00 ± 24.00	0.01** ± 0.00	69.3**	nd	3089.51 × 1565.01	nd	nd	nd

nd = not determined because of insufficient data; C_{max} = maximum concentration after administration; t_{max} = time of maximum concentration; K_{el} = elimination rate constant of the terminal slope of concentration–time curve; $t_{1/2}$ = elimination half-life (Harmonic mean); MRT = mean residence time; $V_{d(area)}$ = apparent volume of distribution using the area method; $V_{d(ss)}$ = apparent volume of distribution at steady-state; Cl = systemic clearance; AUC = total area under the concentration vs. time curve from 0 to infinity. **, Elimination rate could be calculated for only two animals; not sufficient data for other animals; †, there were only two positive tissue samples in this group.

Fig. 1. Plasma concentrations of ticarcillin (solid line) and clavulanate concentrations (dashed line) after i.v. (solid circle) and i.u. administration (open circle) of ticarcillin–clavulanate to mares. Values are shown as means ($\pm$SE). Clavulanate plasma concentrations after i.u. administration are not shown because of insufficient data points.

distribution to the extracellular fluid, because the extracellular fluid rapidly equilibrates with plasma.

The pharmacokinetics of clavulanate after i.v. administration to horses has been previously investigated. The half-life has been reported to be 0.4 h (Sweeney *et al.*, 1988b), and 0.65 h (Sweeney *et al.*, 1988a). In the present study, the mean terminal half-life was calculated to be 0.39 h. In addition, $V_{d(area)}$, and Cl were somewhat lower than what has been reported elsewhere (Sweeney *et al.*, 1988a,b). However, consistent with other investigations in horses, the systemic clearance of clavulanate was faster than clearance for ticarcillin (1.63 vs. 4.05 mL/kg/min).

One objective of this study was to evaluate whether i.v. administration or i.u. administration was superior for producing effective concentrations in endometrial tissues. We compared the tissue concentrations of ticarcillin and clavulanate after i.v. administration of 50 mg/kg ticarcillin, 1.67 mg/kg clavulanate to i.u. administration of 12.41 mg/kg ticarcillin and 0.41 mg/kg clavulanate. As seen in Fig. 2 and Table 1, the tissue concentrations of ticarcillin reached a maximum concentration (C_{max}) that was much higher after i.u. administration of 12.4 mg/kg compared with i.v. administration of 50 mg/kg. Although tissue concentrations after i.u. administration declined at a more rapid rate compared with i.v. administration, the average tissue concentrations after i.u. administration were still higher at 300 min than after i.v. administration. Tissue concentrations of clavulanate after i.v. and i.u. administration were not graphed because there were only two measurable tissue concentrations after i.v. administration. After i.u. administration, clavulanate reached a tissue C_{max} of 8.67 µg/gm compared with a C_{max} of only 0.30 and 0.84 µg/gm in the two positive samples identified after i.v. administration. It is obvious from this study that

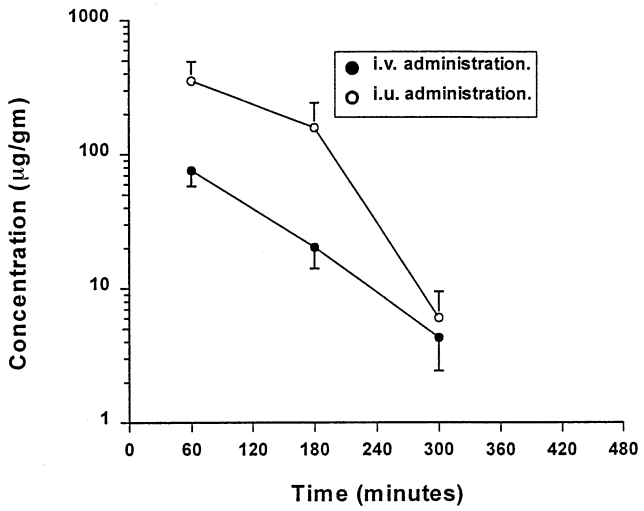

Fig. 2. Ticarcillin tissue concentrations after i.v. and i.u. administration of ticarcillin–clavulanate in mares. Values shown are means (±SE). Clavulanate concentrations are not shown because of insufficient data points.

i.u. administration of the combination of ticarcillin–clavulanate produces higher endometrial tissue concentrations than after i.v. administration, even though for both drugs, lower doses were administered i.u.

One previous study investigated the disposition of ticarcillin in endometrial tissue (Spensely *et al.*, 1986). In that study, it was shown that ticarcillin administered i.u. at a dose of 6 g diluted in either 250 or 60 mL of saline produced tissue concentrations that were >150 μg/gm at 60 min after drug administration. Our study also used 6 g of ticarcillin, which was diluted in 100 mL of saline. However, our study produced much higher tissue endometrial concentrations (C_{max} mean 423.96 μg/gm). This difference in tissue concentrations is probably not caused by a difference in volume into which the drug was diluted because in the previous reported study, peak endometrial concentrations were similar when the drug was diluted in 250 mL as compared with 60 mL (Spensely *et al.*, 1986). However, concentrations persisted longer when the larger volume was administered. Intravenous administration of 30 mg/kg of ticarcillin produced maximal endometrial concentrations of 12.9 μg/gm at 330 min (Spensely *et al.*, 1986). In this study, i.v. administration of 50 mg/kg produced maximal concentrations of 75.98 μg/gm at 60 min. The method used to process the tissue samples should not account for the difference between these studies. The method used in this study, as well as the method used by Spensely *et al.* (1986), measured the drug concentration in a tissue homogenate. Drug concentrations measured in tissue homogenates will underestimate the drug concentration in extracellular fluid because the concentration is diluted in the intracellular fluid that is included in the assay (Cars & Ögren, 1985)

Our results agreed with other investigators that showed that i.u. administration of ticarcillin and clavulanate are absorbed poorly into the systemic circulation after i.u. administration (Threlfall & Keefe, 1983; Sweeney *et al.*, 1984). Plasma concentrations of clavulanate were not detectable after i.u. administration, and plasma concentrations of ticarcillin were high enough in only two mares to calculate systemic availability (8.2 and 3.4%). One author suggested that because of this phenomenon, this is an advantage of an i.u. infusion compared with systemic therapy (Threlfall & Keefe, 1983). With local infusion, most of the drug is expected to remain in the uterus where it is absorbed into the endometrial tissue and is active. If less of the drug is absorbed systemically, this may be beneficial in reducing the emergence of resistance of bacteria in other systems of the body.

After drug absorption into the tissues, the elimination of the drug from the tissue is more rapid than elimination from plasma for ticarcillin (Fig. 2) but slower than elimination from plasma for clavulanate ($t_{1/2}$ 69 vs. 23.1 min). This suggests that i.u. therapy may produce higher concentrations in endometrial tissue compared with i.v. therapy, but does not increase the duration of effective concentrations for ticarcillin.

Because β-lactam antibiotics like ticarcillin are time-dependent antibiotics, drug concentrations should be maintained at the site of infection for as long as possible during a dose interval for a successful cure (Turnidge, 1998). Tissue and plasma concentrations of ticarcillin declined rapidly after i.v. and i.u. administration, as shown in Figs 1 and 2. Therefore, frequent administration of ticarcillin may be necessary to maintain the drug concentration above the minimum inhibitory concentration for susceptible organisms. Because clavulanate concentrations were either low, or persisted for only a short duration in tissue fluid after either route of administration, the addition of clavulanate to this combination for treatment of i.u. infections has questionable value.

ACKNOWLEDGMENTS

The drugs and partial support were provided by SmithKline Beecham Animal Health. Partial support was provided by the North Carolina Veterinary Medical Foundation.

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