Pharmacokinetics of imipenem and cilastatin after their simultaneous administration to the elderly

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1 The pharmacokinetics of imipenem and cilastatin were studied in a group of six healthy elderly male volunteers following the combined intravenous administration of 500 mg imipenem and 500 mg cilastatin sodium as either single or multiple (6 hourly for 6 days) 20 min constant-rate infusions.

2 The pharmacokinetics of both imipenem and cilastatin in the elderly were similar to those of young individuals with mild renal failure (Verpooten *et al.*, 1984).

3 There was no change in the pharmacokinetics of either species with time following multiple-dosing.

4 Correlations existed between total clearance and the glomerular filtration-rate (⁵¹Cr-EDTA) for both imipenem and cilastatin.

Keywords imipenem cilastatin thienamycin elderly volunteers renal function pharmacokinetics

Introduction

Imipenem (thienamycin formamidine) is a relatively new, parenterally administered, broad spectrum antibiotic. Imipenem is a derivative of thienamycin, a natural antibiotic formed by the soil micro-organism, *Streptomyces Cattleya*, and although being a β -lactam antibiotic, differs from the penicillins and cephalosporins by lacking a sulphur atom in the secondary ring. *In vitro* studies have indicated the spectrum of imipenem to include most gram-positive and gram-negative aerobic and anaerobic bacteria (Horadem *et al.*, 1980; Kropp *et al.*, 1980). The broad range of activity is thought to be partially due to a resistance to attack by bacterial β -lactamases (Richmond, 1981).

Preliminary metabolic investigations in man revealed that imipenem is primarily metabolised by the renal dehydropeptidase E.C.3.4.13.11 (Kropp *et al.*, 1982). This metabolic pathway was found to result in low and unpredictable

urinary concentrations of unchanged imipenem. Consequently, imipenem has been administered clinically in combination (1:1) with the renal dehydropeptidase inhibitor cilastatin sodium, resulting in an increase in the renal clearance and urinary recovery of imipenem and an enhanced therapeutic potential (Norrby *et al.*, 1983).

Verpooten *et al.* (1984) have indicated that the pharmacokinetics of both imipenem and cilastatin are markedly affected by decreased renal function. As renal function decreases with age, the potential exists for the pharmacokinetics of both imipenem and cilastatin to be altered in the elderly.

The present investigation was therefore undertaken to investigate the pharmacokinetics of both imipenem and cilastatin in a group of normal 'healthy' elderly (65–75 year old) volunteers following administration as an *i.v.* infusion.

Specifically, we investigated the effect of chronic (6 hourly) 20 min *i.v.* infusions of the imipenem/cilastatin sodium (500 mg:500 mg) combination on the pharmacokinetics of both drugs over a 7 day treatment period, a likely therapeutic regimen.

Methods

Subjects

Six healthy elderly male volunteers took part in the study. Their average height, weight and age were 168 cm (161–174), 64.5 kg (54–77) and 70.2 years (66–75) respectively. All volunteers were judged as being healthy as a result of a physical examination both before and after the study. Pre- and post-study biochemistry and haematology of the volunteers was also found to be normal. Each volunteer was given a detailed description, both verbally and in writing, of the purpose of the study, the discomfort and likely risks involved and the procedures to be followed. Each gave their written informed consent before entering the study. The study was passed by the Medeval Ethics Committee, a voluntary body operating independently of the company.

Prior to the investigation the renal function of the volunteers was assessed by means of their ^{51}Cr -EDTA clearance.

Study design

The study was of a longitudinal design. All subjects entered the study simultaneously and all successfully completed the investigation.

Each subject received 23, 20 min intravenous infusions of 500 mg of imipenem and 500 mg cilastatin sodium over a 7 day period. There was a 12 h interval between the first and second infusions but thereafter the infusions were administered every 6 h. The approximate times of administration were 06.00 h, 12.00 h, 18.00 h and 00.00 h. The volunteers were woken to receive the midnight dose.

The contents of the imipenem/cilastatin sodium vials were thoroughly dissolved in 100 ml of sterile normal saline and administered over a 20 min period using an Imed 960 infusion pump (Imed Ltd, Abingdon, Oxon).

Blood sampling was intensive following the first and last infusion with samples containing peak (immediately following cessation of an *i.v.* infusion) and trough (immediately prior to start of an *i.v.* infusion) concentrations of imipenem and cilastatin being taken on the intermediary days. On the days of intensive blood sampling,

samples were taken immediately prior to and at approximately 10, 20, 30, 45 and 60 min, 1.5, 2, 3, 4, 6 and 8 h following the commencement of the infusion. The plasma obtained from the blood sampling (following centrifugation at 4°C) was divided into two equal aliquots for analysis of imipenem and cilastatin. An equal volume of stabilising solution was added to the aliquot of plasma taken for imipenem analysis. The stabilising solution was prepared by combining, in a 50:50 ratio, ethylene glycol and 0.5 M 4-morpholineethanesulphonic acid (MES; adjusted to pH 6.0 with 1 M NaOH). The stabilised plasma sample and the aliquot taken for cilastatin analysis were immediately stored at -70°C, until analysed.

Blood samples were also collected daily to facilitate the determination of serum creatinine.

Urine was collected in timed aliquots throughout the intensive study periods. The sampling periods were 0–2, 2–4, 4–6, 6–8, 8–10 and 10–12 h following the commencement of the intravenous infusion. On completion of the urine collection associated with a given period, the urine pH was immediately noted and the sample weighed. During a sampling interval the urine container was stored on ice and at the end of a collection period two 10 ml aliquots were removed, one of which was stabilised by the addition of 10 ml of stabilising solution prior to the analysis of imipenem. The urine stabilising solution was a 50:50 mixture of ethylene glycol and 1 M 4-morpholinepropanesulphonic acid (MOPS; adjusted to pH 6.8 with 1 M NaOH). Both urine samples were immediately stored at -70°C until analysed. Solutions of imipenem and cilastatin of known concentration were prepared in both plasma and urine and stored alongside samples obtained from the clinical study.

Drug analysis

Imipenem was analysed in plasma and urine according to the method described by Gravalles *et al.* (1984) and cilastatin according to methodology supplied by Merck, Sharp and Dohme Research Laboratories, Rahway, U.S.A. The methods are described briefly below.

Analysis of imipenem in plasma

The analytical method was based upon reversed-phase h.p.l.c. (100 × 5 mm, 5 µ ODS Hypersil, Shandon Instruments, Runcorn, England) with u.v. absorbance detection at 313 nm. The mobile phase 0.2 M boric acid adjusted to pH 7.2 with

1 M sodium hydroxide, was delivered at a flow rate of 4 ml min⁻¹.

Plasma (1 ml) was prepared for analysis by first spiking with 150 µg internal standard (5-methoxyindole-3-acetic acid; Aldrich Ltd, Gillingham, England) and then deproteinated by ultrafiltration (Amicon Centrifree Micropartition System—centrifugation at 1500 g for 15 min at 4° C). Analysis was performed on the clear ultrafiltrate. Due to the potential instability of imipenem, all samples were stored on ice prior to analysis.

The assay was found to be linear, following spiking of suitable amounts of imipenem to control plasma, over the anticipated *in vivo* concentration range of 5 to 100 µg ml⁻¹ with associated coefficient of variation ($n = 10$) at the extremes being 9.7 and 2.1% respectively.

Analysis of imipenem in urine

Urine analysis of imipenem, although using h.p.l.c. with u.v. absorbance detection, employed a cation-exchange analytical column (250 × 4.6 mm Partisil 10 µ SCX, H.p.l.c. Technology, Macclesfield, England). The mobile phase was prepared by mixing 52 ml of methanol with 2 l 0.5 M boric acid solution and delivered at a flow rate of 2 ml min⁻¹. Sample preparation was as for plasma except that the internal standard was serotonin creatinine sulphate monohydrate (Merck, Sharp and Dohme Research Laboratories, Rahway, U.S.A.). The assay was linear over the concentration range 10 to 100 µg ml⁻¹ with the associated coefficient of variation ($n = 10$) at the extremes being 8.6 and 3.0% respectively. Any *in vivo* urine sample, containing imipenem in a concentration falling above the upper calibrator was suitably diluted with stabilising solution and reanalysed.

Analysis of cilastatin in plasma and urine

Cilastatin was analysed in plasma and urine by reversed-phase h.p.l.c. (250 × 4.6 mm 10 µ Spherisorb ODS 1, Phase Sep Ltd, Queensferry, Wales) with quantification, following post-column derivatisation, by fluorescence detection.

Plasma samples were spiked with 5 µg of internal standard (5-(*p*-methylbenzyl)-L-cysteine; Merck Sharp and Dohme Research Laboratories, Rahway, U.S.A.) mixed with 2 ml 0.5 M KH₂PO₄ solution and placed onto a 'Sep-Pak' (Millipore Waters, Harrow, England) sample preparation cartridge. The cartridge was rinsed

with 20 ml 0.003 M H₃PO₄ and then the sample containing cilastatin and internal standard eluted with 1.5 ml of methanol. One ml of the methanolic eluent was placed into an autosampler vial and diluted with 0.6 ml deionised water prior to analysis. For urine, 1.25 ml of 0.1 M H₃PO₄ was added to 0.5 ml of urine which had previously been spiked (10 µg) with internal standard. After loading the diluted urine onto a 'Sep-Pak' cartridge, sample treatment was as for plasma.

The h.p.l.c. mobile phase consisted of 109 ml propan-2-ol and 2 ml H₃PO₄ (85%) made up to 1 l with deionised water and adjusted to pH 3 with 5 M NaOH. The mobile phase flow-rate was 2 ml min⁻¹. The post-column derivatising reagent was prepared by dissolving 1 g of *o*-phthalic dicarboxaldehyde in 10 ml of absolute ethanol, which in turn was added to 1 l of 0.1 M KOH/borate buffer (pH 7.2). Following degassing by filtration, 0.5 ml of mercaptoethanol was added to the solution which was mixed gently but thoroughly. The post-column flow rate of the derivatising reagent was 1 ml min⁻¹. The mobile phase and post-column derivatising reagent passed through a glass bead packed bed-reactor column prior to entering the fluorimeter (excitation wavelength = 335 nm, emission wavelength = 445 nm).

The assay for cilastatin in both plasma and urine was found to be linear over the anticipated *in vivo* concentration ranges. For plasma the range was 10 to 100 µg ml⁻¹ with associated coefficients of variation of 7.7 and 3.6% respectively ($n = 10$); for urine the range was 25 and 500 µg ml⁻¹ with respective coefficients of variation of 2.7 and 0.8% ($n = 10$). Urine samples containing cilastatin concentrations falling outside the upper calibration concentration were appropriately diluted with blank urine and analysed.

Pharmacokinetic data analysis

The elimination rate constant (k) was obtained by fitting a monoexponential equation to the declining (post-infusion) concentration-time data using unweighted least squares regression. The elimination half-life ($t_{1/2}$) was calculated using the following relationship

$$t_{1/2} = \frac{0.693}{k} \quad (1)$$

and total body clearance (CL) using

$$CL = \frac{\text{Dose}}{\text{AUC}} \quad (2)$$

where Dose is the intravenous dose of either

imipenem or cilastatin and AUC is the area under the plasma drug concentration-time profile from time zero to infinity which for the multiple dosing situation (day 7) was equivalent to a 6 h dosing interval.

The AUC was calculated using the linear trapezoid approximation up to the last time point t , following the first (single) dose and during the dosing interval following the last dose of drug. Following the single dose, the additional area from $t \rightarrow \infty$ was calculated from $C(t)/k$, where $C(t)$ is either the imipenem or cilastatin plasma concentration at time t and k is as previously defined.

Renal clearance (CL_R) was calculated using both plasma and urinary data according to the relationship

$$CL_R = \frac{Ae_{0 \rightarrow t}}{AUC_{0 \rightarrow t}} \quad (3)$$

where Ae and AUC are the amount of drug excreted into the urine unchanged and the area under the plasma drug concentration time-profile respectively, both parameters estimated over an identical time interval of $0 \rightarrow t$ h. For the multiple dose situation the time interval was 6 h (a dosing interval).

The volume of distribution (V) was calculated from

$$V = CL/k \quad (4)$$

Statistical comparisons between the pharmacokinetic parameters defining the disposition of both imipenem and cilastatin following single and multiple *i.v.* dosing were made using a paired Student's *t*-test. Analysis of changes in either peak or trough drug concentrations, following multiple *i.v.* infusions, with respect to time was made by performing a linear regression of peak or trough concentration against time. The regression coefficient was then tested for significance against zero.

Results

Mean plasma drug concentration-time profiles of imipenem and cilastatin following the first and last dose of a 7 day regimen of imipenem: cilastatin sodium (500:500 mg) are shown in Figures 1 and 2. The mean pharmacokinetic parameters defining the disposition of both compounds in the elderly volunteers are listed in Tables 1 and 2. After the first dose, for imipenem total clearance (CL) was $175 \text{ ml h}^{-1} \text{ kg}^{-1}$ (CV(%) 22.9), renal clearance (CL_R) was $94.8 \text{ ml h}^{-1} \text{ kg}^{-1}$ (37.8%), volume of distribution (V) was 0.24 l kg^{-1} (16.7%), and the

Figure 1 Plasma imipenem concentration ($\pm$ s.d.)—time profiles following the first (day 1, Δ) and last (day 7, $\square$) 20 min constant-rate *i.v.* infusion of 500 mg imipenem plus 500 mg cilastatin sodium of a 7 day multiple dosing regimen (500 mg 6 hourly) to six normal, healthy, elderly male volunteers.

Figure 2 Plasma cilastatin concentration ($\pm$ s.d.)—time profiles following the first (day 1, Δ) and last (day 7, $\square$) 20 min constant-rate *i.v.* infusion of 500 mg imipenem plus 500 mg cilastatin sodium of a 7 day multiple dosing regimen (500 mg 6 hourly) to six normal healthy, elderly male volunteers.

half-life ($t_{1/2}$), 0.97 h (18.6%). After the last dose, the values were $CL = 162 \text{ ml h}^{-1} \text{ kg}^{-1}$ (16.8%), $CL_R = 94.6 \text{ ml h}^{-1} \text{ kg}^{-1}$ (37%), $V = 0.24 \text{ l kg}^{-1}$ (12.5%) and $t_{1/2} = 1.07 \text{ h}$ (21.5%). For cilastatin, after the first dose $CL = 119 \text{ ml h}^{-1} \text{ kg}^{-1}$ (30.5%), $CL_R = 64.3 \text{ ml h}^{-1} \text{ kg}^{-1}$ (30.9%), $V = 0.20 \text{ l kg}^{-1}$ (15.0%) and $t_{1/2} = 1.26 \text{ h}$ (31%), and after the last dose, $CL = 110 \text{ ml h}^{-1} \text{ kg}^{-1}$ (27.9%), $CL_R = 73.8 \text{ ml h}^{-1} \text{ kg}^{-1}$ (27.7%), $V = 0.19 \text{ l kg}^{-1}$ (26.0%) and $t_{1/2} = 1.23 \text{ h}$ (28.0%).

The pharmacokinetics of imipenem and cilastatin did not change upon multiple *i.v.* dosing with respect to time (Tables 1 and 2). Furthermore, based upon the lack of change in the daily

Table 1 Mean $\pm$ s.d. pharmacokinetic data prescribing the disposition of imipenem following single (day 1) and multiple (day 7) i.v. infusions to a group of six elderly volunteers

Parameter	First dose (day 1)	Last dose (day 7)	
Elimination rate constant (k ; h^{-1})	0.74 ± 0.13	0.68 ± 0.15	NS
Elimination half-life ($t_{1/2}$; h)	0.97 ± 0.18	1.07 ± 0.23	—
Volume of distribution (V ; 1 kg^{-1})	0.24 ± 0.04	0.24 ± 0.03	NS
Area under the plasma concentration time curve (AUC $0 \rightarrow \infty$; $\text{mg l}^{-1} \text{ h}$)	46.1 ± 7.9	49.1 ± 5.4	NS
Clearance (CL; $\text{ml h}^{-1} \text{ kg}^{-1}$)	175 ± 40	162 ± 27	NS
Fraction of the dose excreted into the urine unchanged (f_e)	0.56 ± 0.13	0.62 ± 0.15	NS
Renal clearance (CL_R ; $\text{ml h}^{-1} \text{ kg}^{-1}$)	94.8 ± 32.8	94.6 ± 34.9	NS

NS = Not significant

Table 2 Mean $\pm$ s.d. pharmacokinetic data describing the disposition of cilastatin following single (day 1) and multiple (day 7) i.v. infusions to a group of six elderly volunteers

Parameter	First dose (day 1)	Last dose (day 7)	
Elimination rate constant (k ; h^{-1})	0.61 ± 0.21	0.60 ± 0.18	NS
Elimination half-life ($t_{1/2}$; h)	1.26 ± 0.39	1.23 ± 0.34	—
Volume of distribution (V ; 1 kg^{-1})	0.20 ± 0.03	0.19 ± 0.05	NS
Area under the plasma concentration time curve (AUC $0 \rightarrow \infty$; $\text{mg l}^{-1} \text{ h}$)	72.2 ± 25.0	76.4 ± 21.6	NS
Clearance (CL; $\text{ml h}^{-1} \text{ kg}^{-1}$)	119 ± 36	110 ± 31	NS
Fraction of the dose excreted into the urine unchanged (f_e)	0.54 ± 0.11	0.69 ± 0.11	NS
Renal clearance (CL_R ; $\text{ml h}^{-1} \text{ kg}^{-1}$)	64.3 ± 19.9	73.8 ± 20.4	NS

NS = Not significant

peak and trough plasma concentrations of imipenem and cilastatin over the 7 day study period, there was no evidence of accumulation of either drug in the elderly (Tables 3 and 4).

A positive correlation was observed between the total clearance of both imipenem ($r = 0.8045$) and cilastatin ($r = 0.8907$) and renal function as determined by ^{51}Cr -EDTA (Figure 3).

Discussion

The mean pharmacokinetic parameters defining the disposition of both imipenem and cilastatin in this group of elderly volunteers most closely resembles those in young patients with mild renal failure (Verpooten *et al.*, 1984). This is not too surprising considering that renal function decreases with increasing age.

The daily trough levels, (pre-infusion), of imipenem and cilastatin are the most sensitive index of the accumulation of either species upon multiple dosing. There was no indication of accumulation, no increase in trough levels with time, of either imipenem or cilastatin upon multiple *i.v.* dosing to elderly volunteers over the 7 day study period (Table 4). The lack of accumulation of either species was further supported by the lack of change, with respect to time, in the peak plasma concentration of both imipenem and cilastatin (Table 3).

The pharmacokinetic parameters defining the disposition of both imipenem and cilastatin showed no difference between the single *i.v.* dose (day 1) and those following multiple *i.v.* dosing (day 7), indicating that the *in vivo* disposition of both species in elderly volunteers did not change with time.

Table 3 Daily peak plasma drug concentrations of cilastatin and imipenem following multiple i.v. infusion of 500 mg imipenem and 500 mg cilastatin sodium to elderly male volunteers

Subject	Day 2	Peak plasma concentration (mg l ⁻¹)				
		Day 3	Day 4	Day 5	Day 6	
<i>Cilastatin</i>						
1	35.82	33.20	—	—	—	
2	48.73	43.65	44.93	45.70	47.93	NS
3	49.05	52.92	56.49	48.16	48.64	NS
4	—	41.01	—	35.68	40.52	NS
5	58.41	63.64	62.94	72.62	55.97	NS
6	70.38	65.88	60.05	66.84	61.35	NS
<i>Imipenem</i>						
1	26.15	28.59	—	—	—	
2	40.28	32.69	36.25	33.88	33.24	NS
3	32.09	38.37	43.02	33.62	34.86	NS
4	30.46	27.98	33.66	22.53	—	NS
5	43.32	46.14	38.82	49.51	33.28	NS
6	35.14	34.95	36.01	41.43	36.98	NS

NS = Not significant

Table 4 Daily trough plasma drug concentrations of cilastatin and imipenem following multiple i.v. infusion of 500 mg imipenem and 500 mg cilastatin sodium to elderly male volunteers

Subject	Day 2	Trough plasma concentration (mg l ⁻¹)				
		Day 3	Day 4	Day 5	Day 6	
<i>Cilastatin</i>						
1	ND	ND	ND	ND	ND	
2	ND	ND	ND	ND	ND	
3	4.16	5.01	4.33	4.15	4.10	NS
4	ND	ND	—	ND	ND	
5	ND	ND	ND	ND	ND	
6	3.31	3.91	3.16	—	3.76	NS
<i>Imipenem</i>						
1	ND	ND	ND	ND	ND	
2	2.68	0.40	0.53	0.27	2.04	NS
3	ND	1.17	1.80	ND	ND	
4	ND	ND	—	ND	ND	
5	1.42	ND	ND	2.69	1.42	NS
6	ND	ND	ND	—	ND	

ND = Non-detectable

— = No sample

NS = No significant difference

Approximately 59% of the administered dose of imipenem and 62% of the administered dose of cilastatin were excreted into the urine unchanged. The clearance of imipenem, and more particularly cilastatin, was highly variable within this group of volunteers. Much of the variability may, however, be captured by differences in renal function within the group. Good correla-

tion existed between total clearance and renal function (⁵¹Cr-EDTA) for both imipenem and cilastatin (Figure 3). Somewhat surprisingly the correlation between renal clearance and renal function was poorer for both imipenem and cilastatin with correlation coefficients (*r*) of 0.73 and 0.48 respectively. The reason for this disparity is unclear but has been observed previously

Figure 3 Relationship between total clearance of imipenem (●) and cilastatin (○) and the renal function (glomerular filtration rate) of six normal, healthy, elderly male volunteers as assessed by ⁵⁷Cr-EDTA.

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