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Comparison of the pharmacokinetics of imipenem after intravenous and intrathecal administration in rabbits

Y. WANG, L. QIU[1], J. DONG, B. WANG, Z. SHI, B. LIU, W. WANG, J. ZHANG, S. CAI, G. YE, X. CAI

Department of Neurosurgery, People's Liberation Army No. 101 Hospital, and [1]School of Medicine and Pharmaceuticals, Jiangnan University, P.R. China

Yuhai Wang and *Liying Qiu* contributed equally to this manuscript

Abstract. – BACKGROUND: Intrathecal administration of antibiotics has potentially high effectiveness for the treatment for severe intracranial infections, particularly nosocomial meningitis. The use of intrathecal injection of antibiotics has been reported mostly in case reports. However, there is sparse data regarding the pharmacokinetics of antibiotics after intrathecal administration.

AIM: This study investigated whether intrathecal injection is an effective method for the administration of imipenem.

MATERIALS AND METHODS: The pharmacokinetics of imipenem after intrathecal and intravenous administration of 1:1 imipenem: cilastatin (IMI/CIL) to rabbits were compared. RESULTS: The AUC_{0-t} in the cerebrospinal fluid for intrathecal administration was approximately twice that of an equal dose of intravenous administration at doses of 0.35, 0.7, and 1.4 mg/kg. Brain concentrations of imipenem after intrathecal injection were three times greater than observed after intravenous injection and remained high for at least 8 hours post-injection. Elimination of imipenem after administration by either route was primarily via urine, but a transient surge of imipenem in bile and intestinal tissue was observed.

CONCLUSIONS: Results indicate that there is a clinical potential for intrathecally administered IMI/CIL. Further studies are warranted to investigate the potential for seizure and to assess the translatability of the rabbit model to human treatment.

Key Words:
Imipenem, Pharmacokinetics, Intrathecal injection, Intracranial infection.

Introduction

Postsurgical nosocomial meningitis is a rare but serious, potentially life-threatening complication of cranial surgery, with a reported incidence ranging from 0.3% to 5.5%[1-6]. Per-operative prophylactic antibiotics are recommended and are effective in decreasing the general rate of incision-related infections.[4] However, while some investigators find prophylaxis to reduce the overall incidence of postsurgical meningitis by almost 50%[7], others report no reduction[4]. Due to the extreme difficulty in treating cranial infections, mortality rates among patients who develop postsurgical meningitis can be as high as 30-40%[2,8].

The pathogens most often responsible for intracranial infections – e.g., *Staphylococcus aureus*, *Acinetobacter* spp, *Pseudomonas aeruginosa*, and coagulase-negative Staphylococci-are often antibiotic-resistant, as a result of the widespread use of broad-spectrum antibiotics[4,6]. It is thought that effective treatment of CNS (central nervous system) infections is also hindered by the difficulty in achieving sufficiently high cerebrospinal fluid (CSF) concentrations of antibiotics, due to the poor ability of most to penetrate the blood-brain barrier[9]. The effectiveness and simplicity of intrathecal administration have encouraged its use as a strategy for achieving therapeutic antibiotic concentrations in CSF[10,11]. However, the pharmacokinetics of intrathecally administered antibiotics is largely unknown.

Imipenem is a β-lactam antibiotic that inhibits cell wall synthesis and has a broad spectrum of activity against aerobic and anaerobic, Gram-positive and Gram-negative bacteria[9,12]. Imipenem remains active in the presence of bacterial beta-lactamase (penicillinase and cephalosporinase) and is a strong inhibitor of beta-lactamases from some Gram-negative bacteria that are resistant to other beta-lactam antibiotics. It is active against *Pseudomonas aeruginosa*, which is associated with rare but often fatal nosocomial meningitis

Corresponding Author: Xuejian Cai, MD; e-mail: cxjxuejian@126.com

following neurosurgical procedures[13]. This study investigated the drug metabolism and tissue distribution of imipenem after intravenous and intrathecal administration of injectable imipenem/cilastatin (IMI/CIL), a formulation combining equal amounts of the imipenem and the renal dehydropeptidase inhibitor cilastatin.

Materials and Methods

Reagents

Imipenem/cilastatin (IMI/CIL) for injection (Tienam®, Lot 100008) was obtained from Merck & Co, Ltd (New Brunswick, NJ, USA); imipenem reference standard was purchased from Chinese CRM/RM Information Center; methanol, acetonitrile, and urethane were purchased from the China National Pharmaceutical Group, AR.

Animal Selection

One hundred twenty healthy Chinchilla rabbits (60 males/60 females; 2 to 3 months old; 2.2 ± 0.5 kg) were provided by Jiangnan Experimental Animal Center (Qualification No. 2004-18). Animals were housed at 25°C in 55% humidity and allowed to acclimate to conditions for seven days before beginning experiments. Food and water were provided *ad libitum*. At the beginning of each protocol, animals were randomly divided into intrathecal and intravenous groups with equal numbers in each group. The protocol was approved by the Institutional Animal Care and Use Committee of the Authors' Institution.

Drug Administration

IMI/CIL was given by either intravenous or intrathecal administration. Intravenous drug was administered through the ear vein. For intrathecal administration, rabbits were placed in the lateral position, and IMI/CIL was injected into the intervertebral space between lumbar and sacral vertebrae. Correct placement of the needle into the spinal canal was judged by whether or not the rabbit displayed an upturned tail or leg twitch, as described by Lv[14]. Doses were administered at a rate of 0.5 mL/min in an injection volume of 0.2 ml/kg for both routes.

Experimental Protocols

The pharmacokinetics of imipenem were evaluated after intravenous and intrathecal administration of IMI/CIL at three doses: 0.35 mg/kg (low), 0.7 mg/kg (medium), and 1.4 mg/kg (high). The doses were selected by converting human doses to an equivalent rabbit dose using data from Dong et al[10]. Each dose was administered intravenously to 12 rabbits and intrathecally to 12 other rabbits. Each group of 12 rabbits was divided into two subgroups of 6 each for sampling of blood and CSF. One subgroup was used for the collection of blood and CSF samples at time 0 and 0.25, 0.5, 1, 2, 4, and 8 hours after drug administration. The second subgroup was used for the collection of blood samples 12 and 24 hours after drug administration.

The distribution of imipenem to major organs of the body was examined over three different time intervals after IMI/CIL (0.7 mg/kg) administration. The drug solution was administered intravenously to 18 rabbits and intrathecally to 18 other rabbits. Six animals from each group were sacrificed at 0.25, 2, and 8 hours after administration. Heart, liver, kidney, spleen, lung, brain, intestine, adipose tissue, and muscle were removed for examination. Each tissue was homogenized in saline to make a 10% homogenate; this was stored at –80°C until analysis.

To examine the elimination of imipenem in feces, urine, and bile, 12 rabbits (6 intravenous, 6 intrathecal) were anesthetized with 5 mL/kg of 20% urethane via ear vein. The rabbits were placed in the supine position, and biliary and urinary catheters were inserted. Feces, urine, and bile were collected over three time intervals: 0-6 hours, 6-12 hours, and 12-24 hours after drug administration.

Sampling and Handling

Blood and CSF samples were obtained from conscious immobilized rabbits. To obtain CSF samples (0.3-0.5 mL), rabbits were placed in a lateral position, and fluid was withdrawn using a syringe inserted into the cisterna magna at a position 0.5 cm below the external occipital protuberance. CSF samples were stored at –20°C until use. At the same time a 1-mL blood sample was withdrawn from the venous catheter, mixed with 1% heparin, centrifuged at 1500 × g for 15 minutes. Plasma was separated and stored at –20°C until use. Before the imipenem assay, blood samples were mixed with 4 volumes of acetonitrile to precipitate proteins, the plasma sample was vortexed for 2 minutes and then centrifuged (12000 rpm for 10 minutes), and the resulting supernatant was filtered through a 0.45 μm microfiltration membrane. A 15 μl aliquot was used for imipenem determination.

Bladder and bile duct intubations were performed, and urine and bile samples were collected while the animals were under anesthesia. Urine and bile samples (200 μL) were filtered through 0.45 μm membranes. The filtrate was then mixed with 20 μL acetic acid in a 10-mL stoppered test tube, after which 4 mL of ethyl ether was added and the mixture was vortexed for 3 minutes. The supernatant was dried under nitrogen flow in a water bath at 60°C and dissolved in 100 μL methanol. A 15 μL aliquot of the sample was withdrawn for imipenem determination.

Collected fecal matter was dried under an infrared lamp, weighed, and ground into a powder. A fecal homogenate was prepared by adding 4 mL of 0.9% NaCl to 100 mg of fecal powder, mixed with 20 μL acetic acid in a 10 mL stoppered test tube, and centrifuged at 3000 rpm for 10 minutes. A 1 mL aliquot of the supernatant was mixed with 4 mL of ether in a 10 mL stoppered test tube and vortexed for 3 minutes. The resulting supernatant was dried by nitrogen in a 60°C water bath, and dissolved in 100 μL methanol. A 15 μl aliquot was used for imipenem determination.

For the analysis of imipenem in tissues, 100 mg of tissue was homogenized in 0.9 mL saline, centrifuged at 3000 rpm for 10 minutes, and 200 μL of supernatant was filtered through a 0.45 μm filter membrane. The filtrate was placed in a10-mL stoppered test tube and mixed with 20 μL of 10% perchloric acid. Ether (4 mL) was added and the mixture was vortexed and centrifuged for 3 minutes. The supernatant was placed in a 60°C water bath, dried under nitrogen flow, and then dissolved in 100 μL methanol. A 15 μL aliquot was used for imipenem determination.

Imipenem Determination

A reference standard solution of 1 mg/mL imipenem with stabilizer was prepared as described in the US Pharmacopeia (2005 edition). In addition, an internal standard solution of 50 μg/mL 5-hydroxyindole acetic acid in methanol was prepared. The following HPLC conditions were used: C18 column (3.9 × 250 mm, 10 μm particle size; Agilent, Shanghai); methanol (1.0 mM): KH_2PO_4 (5:95 v/v as mobile phase); flow rate 1.0 mL/min; detection wavelength 298 nm; column temperature 32 ± 1°C; injection volume 15 μl.

To determine the accuracy of the HPLC detection method for imipenem, reference solutions of 400, 200, 100, 50, and 25 μg/ml were prepared, and 15 μL aliquots of each was injected into the HPLC. Chromatographic peak areas were measured, and a plot of peak area vs. concentration curve was constructed. A significant linear relationship was observed between concentration and peak area, with the fitted line of area = 6.1542 + 3.8083 * concentration ($R^2 = 0.99989$) (Figure 1). A linear relationship was observed between peak area and injection doses of 0.375 to 6 μg imipenem, and the minimum detection limit was 2.5 μg/mL.

Calculation of Pharmacokinetic Parameters

The software system DAS2.1.1 was used for pharmacokinetic simulations and to calculate the following pharmacokinetic parameters: $t_{1/2\alpha}$ (drug distribution phase half life); $t_{1/2\beta}$ (plasma drug elimination half-life); V1/F (volume of distribution); CL/F (apparent clearance rate); $AUC_{(0\text{-}t)}$ (plasma concentration/time, area under the curve); K10 (apparent first-order rate constant of elimination of drug from the vascular compartment); k12 (rate constant for the transfer of drug from vascular compartment to CSF); k21 (rate constant for the transfer of drug from the CNS to vascular compartment); ka (absorption rate constant). $AUC_{(0\text{-}\infty)}$ refers to the AUC from time zero to the time at which all prototype drugs are totally eliminated, reflecting the total amount of drug in the blood.

Statistical Analysis

Data were expressed as mean ± standard deviation. The difference between the results from intravenous vs. intrathecal routes of administration was assessed using the independent two sample *t*-test. Within-group data were analyzed using the paired *t*-test. Simple linear regression was performed to evaluate the relationship between imipenem concentration and the peak area. Values of $p < 0.05$ were considered statistically significant. However, for the group comparisons of the pharmacokinetics parameters at three various dosages, the significance level was adjusted as 0.0167 to control the family-wise error rate under 0.05. All statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, USA).

Results

Imipenem Levels in Brain.

Brain concentrations of imipenem were significantly higher 0.25, 2, and 8 hours after intrathe-

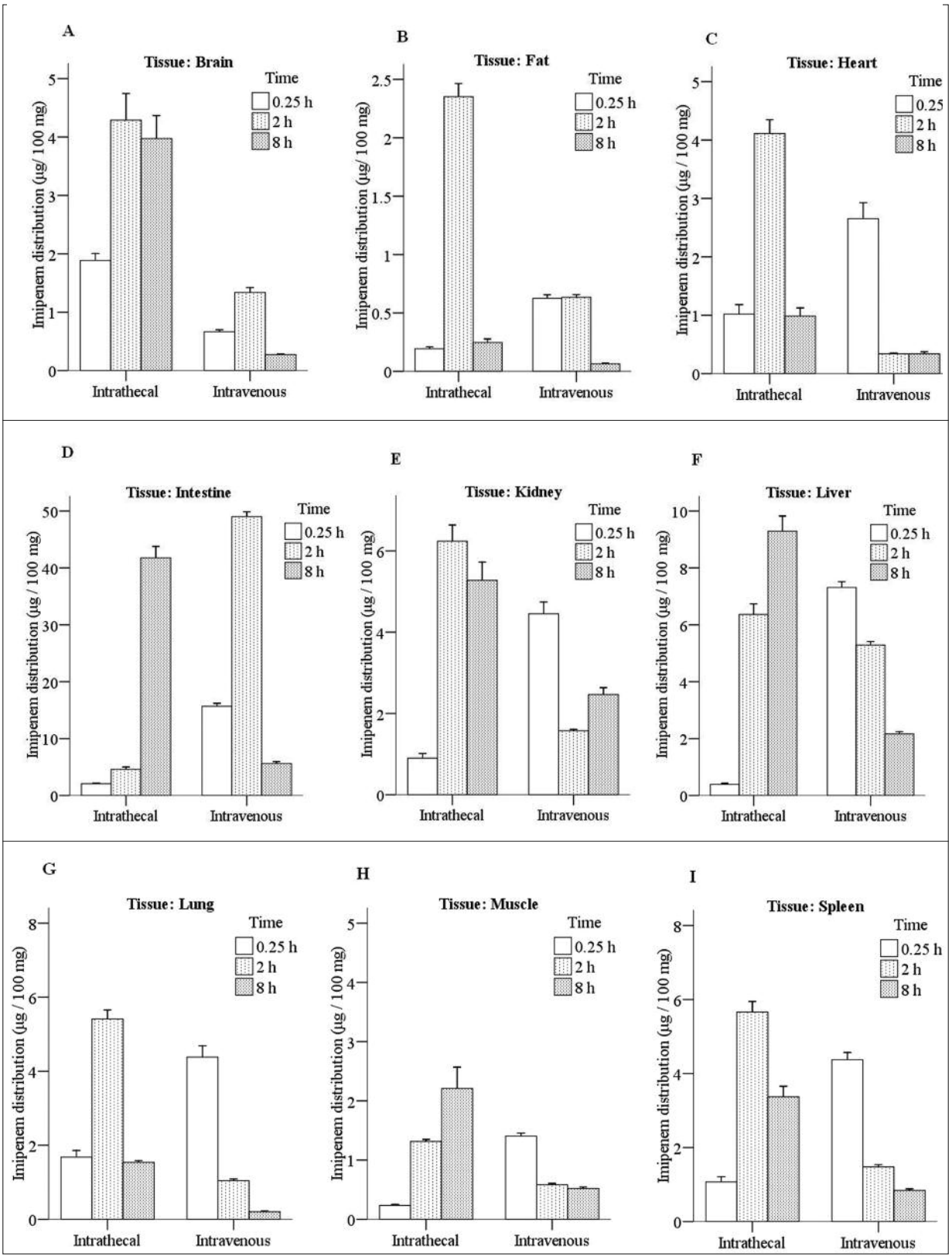

Figure 1. Imipenem distribution in various tissues. ***A,*** Brain. ***B,*** Fat. ***C,*** Heart. ***D,*** Intestine. ***E,*** Kidney. ***F,*** Liver. ***G,*** Lung. ***H,*** Muscle. ***I,*** Spleen.

Figure continued

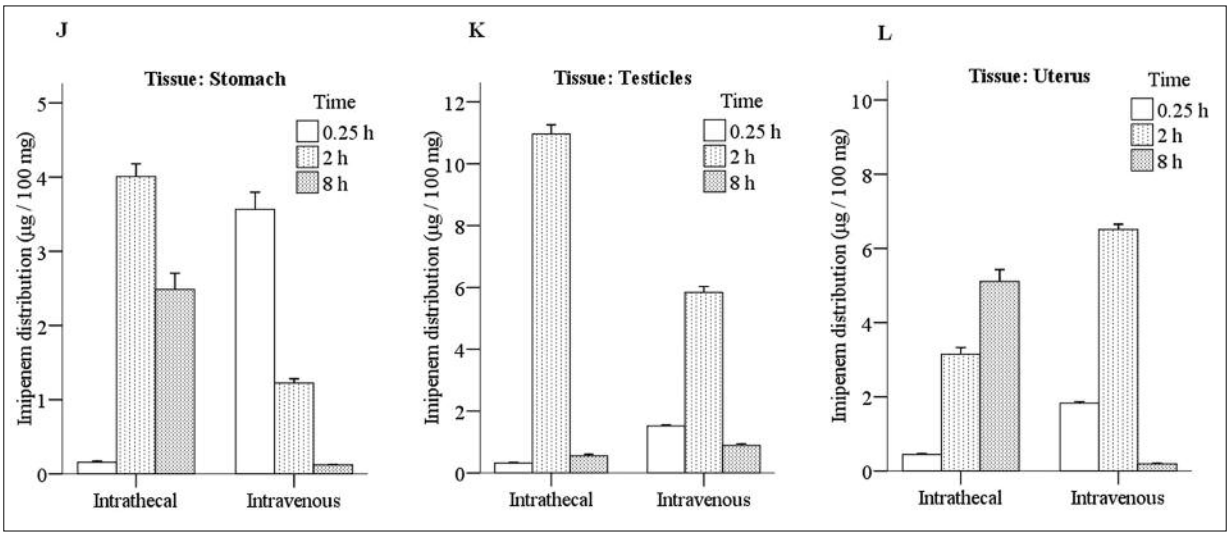

Figure 1. ***(Continued). J,*** Stomach. ***K,*** Testicles. ***L,*** Uterus. All of the comparisons between intrathecal and intravenous groups at 0.25, 2, 8 hours after administration obtained statistical significance ($p \leq 0.001$).

cal administration of IMI/CITL compared to the corresponding times after intravenous administration (Figure 1A). The brain level of imipenem following intrathecal IMI/CIL administration peaked at 2 hours and showed no significant decline after 8 hours. In contrast, following intravenous administration the peak concentration at 2 hours reached only about 30% of that after intrathecal administration and fell to nearly undetectable levels by 8 hours.

Plasma Half-life and Volume of Distribution

The imipenem plasma $t_{1/2\alpha}$ was significantly longer following intrathecal IMI/CIL administration compared with intravenous administration at all doses, but the elimination half-lives ($t_{1/2\beta}$) were similar for the two dosage methods except, at the low 0.35 mg/kg dose (Table I). The volumes of distribution calculated from plasma data were lower for intrathecal than intravenous imipenem, and this difference reached statistical significance at the low dose. At the low dose, intrathecally administered imipenem also showed a significantly longer elimination half-life and lower volume of distribution than intravenously administered imipenem.

Plasma AUC, Clearance, and Rate Constants

The plasma AUC for imipenem increased with dose after both intrathecal and intravenous administration. However, the plasma imipenem $AUC_{0\text{-}t}$ showed a proportional, 4-fold increase over the dose range after intravenous IMI/CIL administration, whereas the imipenem $AUC_{0\text{-}t}$ only doubled after intrathecal drug administration (Table I). Plasma imipenem clearance also increased with dose for both intrathecally and intravenously drug administration. Imipenem clearance rose more sharply with dose after intrathecal drug administration than with intravenous dosing (Table I). No significant differences in the elimination rate constant (K10) were observed between intravenous and intrathecal administration at the lower doses, but K10 was significantly greater for the intrathecal route at the highest dose. The rate constants K12 (vascular compartment to CSF) and K21 (CSF to vascular compartment) were both lower for intrathecal than for intravenous administration.

CSF Parameters

Measurement of imipenem in the CNS revealed significantly higher levels after intrathecal drug administration for all doses compared with intravenous administration (Table II). Rate constants were similar for both methods of administration, except for the K21 rate constant at the 0.7-mg/kg dose (Table II).

Tissue Uptake and Excretion

The maximum accumulation of imipenem in most tissues examined was relatively low (1 to 10 µg/100 mg tissue) and tended to occur during the early time period (0-0.25 hours) for intravenously administered drug and during the middle time

Table I. Summary of pharmacokinetic parameters for plasma.

Parameters	Dose (mg/kg)	Group Intrathecal (n = 6)	Intravenous (n = 6)	*p*-value
$t_{1/2\alpha}$ (h)	0.35	0.778 ± 0.152	0.398 ± 0.050	0.001*
	0.7	0.990 ± 0.163	0.647 ± 0.206	0.010*
	1.4	1.208 ± 0.452	0.701 ± 0.210	0.032
$t_{1/2\beta}$ (h)	0.35	18.062 ± 3.881	9.624 ± 1.492	0.001*
	0.7	6.752 ± 1.060	7.190 ± 1.993	0.648
	1.4	10.307 ± 5.797	6.622 ± 0.535	0.181
V1/F (L/kg)	0.35	0.125 ± 0.010	0.401 ± 0.067	< 0.001*
	0.7	0.200 ± 0.060	0.387 ± 0.134	0.017
	1.4	0.296 ± 0.095	0.406 ± 0.079	0.055
CL/F (L/h/kg)	0.35	0.040 ± 0.004	0.088 ± 0.009	< 0.001*
	0.7	0.065 ± 0.005	0.080 ± 0.006	0.001*
	1.4	0.110 ± 0.016	0.087 ± 0.008	0.010*
$AUC_{(0-t)}$ (mg/L·h)	0.35	6.405 ± 0.663	3.225 ± 0.283	< 0.001*
	0.7	9.758 ± 0.860	7.586 ± 0.578	< 0.001*
	1.4	12.129 ± 1.351	13.976 ± 1.175	0.030
$AUC_{(0-\infty)}$ (mg/L·h)	0.35	8.763 ± 0.867	3.967 ± 0.423	< 0.001*
	0.7	10.839 ± 0.908	8.757 ± 0.745	0.001*
	1.4	12.883 ± 1.618	16.173 ± 1.507	0.005*
K10 (h-1)	0.35	0.292 ± 0.063	0.227 ± 0.030	0.047
	0.7	0.342 ± 0.074	0.233 ± 0.087	0.040
	1.4	0.368 ± 0.075	0.230 ± 0.026	0.005*
K12 (h-1)	0.35	0.383 ± 0.111	1.257 ± 0.324	< 0.001*
	0.7	0.288 ± 0.171	1.450 ± 0.313	< 0.001*
	1.4	0.203 ± 0.170	0.909 ± 0.134	< 0.001*
K21 (h-1)	0.35	0.131 ± 0.036	0.537 ± 0.132	< 0.001*
	0.7	0.206 ± 0.069	0.624 ± 0.191	0.002*
	1.4	0.169 ± 0.113	0.444 ± 0.102	0.001*
Ka (h-1)	0.35	1.272 ± 0.220		
	0.7	0.931 ± 0.201		
	1.4	1.692 ± 1.132		
$t_{1/2Ka}$ (h)	0.35	0.523 ± 0.138		
	0.7	0.769 ± 0.141		
	1.4	0.615 ± 0.330		

The significance level was adjusted as 0.0167 to control the family-wise error rate under 0.05. Data was expressed by mean ± standard deviation. *Indicates a significant difference in the corresponding parameter was observed.

period (0.25-6 hours) for intrathecally administered drug. Brain tissue was an exception, as discussed above, where peak levels occurred at the 2-hour measurement for both routes of administration. A more notable exception was seen in the intestine, where the maximum uptake was considerably higher (42-48 μg/100 mg tissue) for both methods of administration and was reached at later times (6 hours, intravenous; 8 hours, intrathecal) (Figure 1).

Imipenem was eliminated primarily in urine, except for peaks in bile concentration observed at 0-6 hours for intravenous and 6-12 hours for intrathecal administration (Table III). Both peaks were accompanied by a small amount of fecal imipenem (Table III). The maximum imipenem concentration in intestinal tissue occurred during the same times as the peaks in biliary concentration.

Discussion

Intrathecal administration of IMI/CIL produced brain imipenem levels that were 3-fold higher and sustained for at least four times the duration of levels achieved by intravenous dosing. The extended brain exposure time achieved by intrathecal dosing is critically important in treating severe cases of postsurgical meningitis.

Imipenem, is a β-lactam antibiotic characterized by minimal concentration-dependent

Table II. Summary for the pharmacokinetics parameter in cerebrospinal fluid.

Parameters	Dose (mg/kg)	Group Intrathecal (n = 6)	Intravenous (n = 6)	*p*-value
$t_{1/2\alpha}$ (h)	0.35	0.652 ± 0.194	6.880 ± 2.554	< 0.001*
	0.7	43.169 ± 15.886	14.249 ± 2.241	0.006*
	1.4	29.254 ± 4.786	13.341 ± 2.192	< 0.001*
$t_{1/2\beta}$ (h)	0.35	167.847 ± 31.874	6.969 ± 2.398	< 0.001*
	0.7	43.229 ± 16.084	14.279 ± 2.254	0.007*
	1.4	30.511 ± 7.941	13.370 ± 2.237	0.002*
$V_{1/F}$ (L/kg)	0.35	3.085 ± 0.793	3.105 ± 1.255	0.976
	0.7	1.811 ± 1.649	5.487 ± 0.436	0.002*
	1.4	5.909 ± 2.495	9.774 ± 0.716	0.004*
CL/F (L/h/kg)	0.35	0.043 ± 0.016	0.290 ± 0.060	< 0.001*
	0.7	0.085 ± 0.044	0.318 ± 0.025	< 0.001*
	1.4	0.188 ± 0.041	0.584 ± 0.063	< 0.001*
$AUC_{(0-t)}$ (mg/L*h)	0.35	2.554 ± 0.091	1.136 ± 0.353	< 0.001*
	0.7	3.169 ± 0.248	1.820 ± 0.113	< 0.001*
	1.4	3.844 ± 0.140	1.976 ± 0.120	< 0.001*
$AUC_{(0-\infty)}$ (mg/L*h)	0.35	9.048 ± 3.096	1.265 ± 0.338	0.005*
	0.7	10.975 ± 6.694	2.213 ± 0.187	0.024
	1.4	7.795 ± 2.026	2.419 ± 0.252	0.001*
K10 (1/h)	0.35	0.015 ± 0.008	0.121 ± 0.083	0.021
	0.7	0.097 ± 0.078	0.058 ± 0.007	0.277
	1.4	0.075 ± 0.074	0.060 ± 0.009	0.657
K12 (1/h)	0.35	0.436 ± 0.599	0.058 ± 0.074	0.231
	0.7	0.244 ± 0.452	0.011 ± 0.019	0.263
	1.4	0.106 ± 0.130	0.011 ± 0.022	0.135
K21 (1/h)	0.35	0.871 ± 0.545	0.119 ± 0.071	0.036
	0.7	0.147 ± 0.052	0.050 ± 0.009	0.005*
	1.4	0.268 ± 0.405	0.053 ± 0.009	0.250
Ka (1/h)	0.35	1.109 ± 0.276		
	0.7	2.080 ± 2.891		
	1.4	1.695 ± 0.762		
$t_{1/2Ka}$ (h)	0.35	0.663 ± 0.196		
	0.7	0.731 ± 0.558		
	1.4	0.489 ± 0.176		

The significance level was adjusted as 0.0167 to control the family-wise error rate under 0.05. Data was expressed by mean ± standard deviation. *Indicates a significant difference in the corresponding parameter was observed.

killing[9]. The bactericidal activity of this class of antibiotics is not dose-dependent, but instead, maximal bactericidal efficacy is seen at low multiples of the minimal bactericidal dose and is achieved by extending the time of bacterial exposure to effective concentrations[15]. For

Table III. Summary of the excretion pathway of imipenem.

Time		Intrathecal (n = 6)	Intravenous (n = 6)	*p*-value
0-6h	Excrement (mg/g)	–	0.0497 ± 0.0006	
	Urine (mg/ml)	7.57 ± 0.60	7.61 ± 0.27	0.9170
	Bile (mg/ml)	1.57 ± 0.18	13.45 ± 0.32†,‡	< 0.001*
6-12h	Excrement (mg/g)	0.0504 ± 0.0006	–	
	Urine (mg/ml)	7.55 ± 0.57	5.12 ± 0.21	0.002*
	Bile (mg/ml)	5.33 ± 0.36	1.83 ± 0.07‡	< 0.001*
12-24h	Urine (mg/ml)	1.25 ± 0.23	0.06 ± 0.00	0.012*
	Bile (mg/ml)	0.4831 ± 0.0253‡	0.0710 ± 0.0010	0.001*

*Indicates a significant difference was observed between groups. ‡Indicates a significant difference as compared to urine within group was observed.

imipenem, exposure times equivalent to at least 40% of the dosing interval are recommended[9]. Although the present data from rabbits do not allow us to make a direct prediction about the brain levels or duration that could be achieved from intrathecal administration in humans, it is likely that our data reflect the magnitude of exposure that could be gained intrathecal IMI/CIL administration in humans.

Differences Between Intravenous and Intrathecal Kinetics

After intravenous injection of IMI/CIL, imipenem is rapidly distributed in the cardiovascular space, and from this compartment is both distributed to the extravascular space and eliminated from the body. Intrathecal administration is quite different. In humans the CSF represents a small (150 mL) drug metabolism-free compartment, relative to the vascular (3 L) and extravascular water (15 L) compartments, and the relative sizes of these compartments are comparable in rabbits. This time-dependent delivery of drug to the vascular compartments observed after intrathecal administration is similar to what is observed with slow-release oral formulations. This slow, continuous transfer of imipenem from the CNS to vascular space accounts for the increased plasma distribution half-life with intrathecal administration.

The percent increase in plasma AUC with increasing dose was smaller for intrathecal than intravenous injections, where the increase in AUC was dose-proportional. Similar results have been reported after intravenous dosing in humans[16,17]. Clearance increased more sharply with dose after intrathecal administration. This sharper increase in clearance with dose probably explains the smaller increase in AUC seen with intrathecal injection.

CSF Pharmacokinetics

The AUC in the CSF after intrathecal injection was approximately twice that seen after intravenous injection, a result not seen with plasma AUC. The standard deviations for the intrathecal CSF data were large, and may indicate the amount of drug delivered to the brain from the spinal injection site may be variable. Alternatively, the variability may reflect the statistical model used. The program used to determine pharmacokinetic parameters from CSF data was not designed to model the geometry involved, i.e., a small, relatively impermeable CNS compartment connected to a large vascular compartment, and connected in turn to an even larger extravascular compartment. Orsini et al[18] modeled a similar system involving imipenem concentrations in plasma and synovial fluid compartments in horses. Their simulation revealed a slower increase to maximum and a slower decrease after maximum in synovial fluid than in plasma after intravenous drug administration. Our data show a longer elimination $t_{1/2}$ in CSF than in plasma for the two highest drug doses, but not for the lowest dose. Our study simulates the reverse condition-drug injected into the small CSF compartment and draining outward into 2 large compartments-which was not modeled by the Orsini group.

Elimination and Organ Uptake

Imipenem, whether injected intravenously or intrathecally, was eliminated primarily in the urine. This is similar to what is described for imipenem in humans, where a 64-67% urinary recovery of imipenem has been reported after IMI/CIL administration[16,17]. Human studies show that inhibition of enzymatic breakdown by cilastatin is not always complete, but our study did not address this question. In humans, less than 2% of imipenem is recovered from feces, so it is thought that biliary excretion is negligible[17]. We also found only a small amount of imipenem in feces, but found high concentrations in bile and intestinal tissue during two time intervals, 0-6 hours for intravenously administered imipenem, and 6-12 hours for intrathecally administered imipenem. Since intestinal absorption of imipenem in humans is thought to not occur[12], this may reflect a peculiar feature of our rabbit model.

Clinical Implications

Our data clearly indicate that intrathecal administration is effective at achieving significantly higher brain exposure to imipenem for a longer duration than can be attained with intravenous dosing. Our CSF intrathecal data suggests that delivery of imipenem CSF to other compartments may be variable, but the consistency of our brain-exposure results indicate that reproducibly high brain exposure can be achieved. We studied the pharmacokinetics of imipenem in healthy rabbits, and it is difficult to say how they might change in the presence of infection. We also do not know how the permeability of the blood-brain barrier to imipenem is affected by intracranial infection

when the meninges are likely inflamed. It has been suggested that the alterations in the blood-brain barrier occurring during surgery increase its permeability to antibiotics[4], and if this is true it could hasten the transfer of imipenem from the CSF to the vascular compartment in cases of postsurgical meningitis. Seizures are also known to occur rarely with intravenous imipenem, at a rate of about 0.24%[9]. We do not know whether or to what extent the risk of seizures might increase after intrathecal delivery.

Conclusions

Compared with intravenous administration, intrathecal administration of imipenem-cilastatin achieves a higher CSF concentration and brain exposure to imipenem, as well as a much longer duration and slower elimination. During intrathecal administration, drug concentration peaks in other tissues appear later than via intravenous administration. The improved pharmacokinetic profile observed after intrathecal administration will allow central minimal bactericidal concentrations to be achieved and maintained for longer durations, allowing for more effective treatment of postsurgical nosocomial meningitis.

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