Pharmacokinetics of Meropenem in Patients with Liver Disease

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Eight subjects with chronic stable alcoholic cirrhosis and eight matched controls with normal liver function were given an initial 30-minute intravenous infusion of 1 g of meropenem; beginning 24 hours later, they received five additional 1-g doses at 6-hour intervals. No statistically significant differences were found between the first dose and steady state or between groups for any plasma pharmacokinetic parameters—including the highest observed plasma concentrations, plasma concentrations at 6 hours after dosing (C_{th}), terminal half-life, area under the plasma concentration—time curve (AUC), area under the first moment of the curve, plasma clearance, steady-state volume of distribution, and accumulation ratios—on the basis of either AUC or C_{th}. There were also no statistically significant differences in any of the measured or calculated pharmacokinetic parameters of the microbiologically inactive metabolite of meropenem (ICI 213,689). A total of 11 adverse experiences (one moderate and 10 mild) were reported by four patients; nine of these experiences, including two in controls, were rated by the investigator as "possibly" drug related. It is concluded that meropenem is well tolerated with repeated intravenous dosing and that dosage adjustments are not necessary for patients with hepatic disease.

Meropenem is a new carbapenem antibiotic with broad-spectrum activity against a wide variety of gram-positive and gram-negative aerobic and anaerobic pathogens. It is now under development for treatment of severe infections in adults and children that are due to bacteria that may be resistant to currently available antibacterial agents or combinations of these agents. In previous clinical pharmacology studies in which parenteral meropenem was administered [1-4], this drug was well tolerated after administration of single and multiple doses.

The elimination half-life of meropenem is ~1 hour in healthy subjects, while that of its open-ring metabolite (ICI 213,689, a microbiologically inactive form) is ~2 hours [3, 5]. The area under the plasma concentration—time curve (AUC) shows an approximately linear relationship with doses ranging from 0.25 to 1 g. The major route of excretion is renal, with 60% to 80% of meropenem being recovered unchanged in urine. In radiolabeled drug studies [3], about 90% of the dose was accounted for as meropenem and ICI 213,689 in urine. Approximately 1% to 2% of the dose is excreted in feces over a 7-day period. Plasma protein binding in humans is ~2%.

The mechanism by which meropenem is transformed to ICI 213,689 in humans is currently unknown. The open-ring metabolite may be formed by cleavage of the β-lactam bond by an enzyme system or by chemical hydrolysis. The role of non-microsomal enzymes in liver metabolism is unknown.

Although repeated dosing with meropenem has not been associated with significant alterations in liver function in humans, the effect of liver disease on the disposition of meropenem has not previously been systematically studied. Therefore, the purpose of the study reported here was to compare the pharmacokinetics of meropenem in subjects with stable hepatic disease and in those with normal hepatic function.

Methods and Materials

This study was a 5-day open-label trial of multiple intravenous doses of meropenem for subjects with chronic stable hepatic disease (cases) and for age-matched (±2 years), weight-matched (±10%), and sex-matched subjects without hepatic disease (controls). The study protocol and informed consent form were approved by the First Foundation for the Protection of Human Subjects in Research, and informed written consent was obtained from each subject before study entry.

Patients.

Patients with hepatic disease were enrolled in the study if they were between the ages of 18 and 65 years, had a body weight within 15% of their ideal weight, and had a history of chronic stable hepatic disease documented by clinical and laboratory findings and confirmed by biopsy. Patients of both sexes were eligible for enrollment, but women who could bear children were excluded.

Other exclusion criteria included significant deviations from normal findings of clinical laboratory tests, physical examination, chest roentgenograms, or electrocardiogram; a history of significant clinical renal, hematologic, endocrine, cardiovascular, gastrointestinal, metabolic, neurological, or chronic respiratory disease; or recent changes in hepatic function in patients with hepatic disease. Acute illness within 7 days of study.
enrollment or a history of psychiatric disease, epilepsy, head
trauma, organic brain disease, recent neurosurgery, allergy to
β-lactam antibacterials, or asthma was also grounds for exclu-
sion.

Patients were not allowed to take barbiturates or other drugs
affecting the liver’s drug-metabolizing enzymes or to have
made a blood donation or participated in another clinical drug
study within 4 weeks of enrolling in the current study. Subjects
with hepatic disease were allowed to take medication before
and during the study provided that the medication did not affect
hepatic drug metabolism or renal tubular secretion.

Laboratory tests. Hematology and blood chemistry tests
were conducted on blood samples obtained after an 8-hour fast
at the screening examination and before dosing on study days
2 and 3 and including the following: RBC, WBC, differential,
and platelet counts; hematocrit; prothrombin time; and deter-
nations of hemoglobin, aspartate transaminase (AST), alanine
transaminase (ALT), alkaline phosphatase, total bilirubin, urea
nitrogen, creatinine, glucose, uric acid, triglyceride, sodium,
potassium, chloride, total protein, albumin, calcium, and phos-
phorus levels. Urine samples, obtained at screening and before
dosing on days 2 and 3, were tested for pH, specific gravity,
and levels of protein, glucose, ketones, and occult blood; a
complete microscopic examination of urine sediment was per-
formed.

Clinical examination. Patients were screened for subjective
symptoms when vital signs were recorded. Adverse experiences
were recorded, and the relationship of these events to drug
administration was assessed by the investigators. Supine and
standing blood pressure, heart rate, supine respiratory rate,
weight, and oral temperature were measured during the screen-
ing examination and on study day 5. Blood pressure, heart rate,
and supine respiratory rate were also determined before the
third and fourth doses of meropenem and at 6 hours after the
final dose. Patients refrained from heavy smoking, caffeine
consumption, alcohol consumption (from 7 days before study
entry), medication use (except as noted), rigorous exercise,
sunbathing, saunas, or steam baths during the study.

Drug administration. Meropenem was supplied as a sterile
blend of meropenem powder and sodium carbonate (molar ratio,
1:0.75), and doses were prepared by dissolving the powder in
sterile saline solution (0.9% sodium chloride for injection) at the
study site immediately before dosing on study days 2, 3, and 4.
Doses were prepared as intravenous infusion solutions, with each
infusion bag containing 250 mL of dosing solution with a mero-
penem concentration of 5 mg/mL. Each dose (200 mL containing
1 g of meropenem) was administered over a 30-minute period
via an IMED infusion pumping system (IMED, San Diego).
Starting 24 hours after the day 2 dose, meropenem was given at 6-
hour intervals. A total of six doses were infused. Subjects were
confined to the clinical research center from the evening of day
1 until the morning of day 5, where they received standardized
meals and fasted for 8 hours before and 4 hours after the first
and sixth doses.

Sampling. Pharmacokinetic parameters for meropenem
and its metabolite ICI 213,689 were determined in blood and
urine samples obtained immediately before the morning infu-
sion of study medication, 15 minutes after the start of infusion
and immediately upon the conclusion of infusion, as well as
at 35 and 45 minutes and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8,
10, 12, 16, and 24 hours after the beginning of the first and sixth
doses. Blood samples (6 mL) were collected in heparinized
evacuated tubes, thoroughly mixed, and centrifuged immedi-
ately. Plasma samples were transferred into polypropylene
tubes, rapidly frozen in dry ice, and maintained at −70°C until
they were analyzed. Urine samples were collected just before
the first dose and during intervals from 0 to 1, 1 to 2, 2 to 3,
3 to 4, 4 to 6, 6 to 12, and 12 to 24 hours after the first and
sixth doses. After the start of the second dose (on day 3), a
24-hour collection also was made. Urine was pooled, mixed,
and refrigerated; aliquots were frozen and maintained at −70°C
until they were analyzed.

Assay procedures. Assays were performed by the Drug
Disposition and Metabolism Department of Zeneca Pharmaceu-
ticals by using a reverse-phase HPLC method (ICI procedure
number 24P-01[R2]) previously validated for the analysis of
meropenem in plasma; this method had a quantification limit
of 0.5 μg/mL. Data on assay variability are presented in table
1. An ion-exchange HPLC system with a silica column (mobile
phase, 0.1% phosphoric acid in water) was used for the analysis
of meropenem in urine (ICI procedure number 24U-03[R1]);
the quantification limit of this method was 1.0 μg/mL. An RIA
method was used for the analysis of ICI 213,689 in plasma
and urine.

Pharmacokinetic analysis. Plasma meropenem concen-
tration vs. time data were evaluated by noncompartmental
methods. Plasma meropenem concentration–time data for study
days 2 and 4 were analyzed by nonlinear least-squares regres-
sion with use of a weighting scheme of 1/y or 1/y² (where y
refers to the observed plasma concentration) for calculation of
terminal half-life (t½). The AUC and the area under the first
moment of the curve (AUMC) were estimated for both mero-
penem and ICI 213,689 by the trapezoidal rule; values were
then extrapolated to infinity.

The plasma clearance of meropenem (Clp) following the first
dose was calculated from the ratio of the nominal dose to
AUC₀–∞ , and the Clp following the last dose was determined
as the ratio of dose to AUC₀–6h , where AUC₀–6h is the AUC
bounded by the final 6-hour dosing interval. The steady-state
volume of distribution (Vss) was determined after administra-
tion of the first dose of meropenem according to the equation
Vss = (dose × AUMC₀–∞)/(AUC₀– ☐), where T is the duration of the infusion (0.5 hour).
The accumulation of meropenem and ICI 213,689 following
repeated administration was assessed by using two equations:
R = steady-state AUC₀–6h/first-dose AUC₀–6h or R = steady-
state C₀–6h/first-dose C₀–6h, where R is the accumulation ratio and
C₀–6h is the plasma concentration at 6 hours after dosing.
Table 1. Precision of within-day and between-day assays for meropenem and its metabolite (ICI 213,689) in plasma and urine.

<table>
<thead>
<tr>
<th>Precision (percentage RSD)</th>
<th>Plasma</th>
<th>Urine</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Within-day assay</td>
<td>Between-day assay</td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Medium</td>
<td>3.8</td>
<td>4.1</td>
</tr>
<tr>
<td>High</td>
<td>2.8</td>
<td>4.1</td>
</tr>
<tr>
<td>ICI 213,689</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Medium</td>
<td>5.1</td>
<td>9.4</td>
</tr>
<tr>
<td>High</td>
<td>3.4</td>
<td>8.4</td>
</tr>
</tbody>
</table>

NOTE. NA = not available; RSD = relative standard deviation.

The effective half-life (t_{1/2eff}) of ICI 213,689 was calculated according to the equation $t_{1/2\text{eff}} = (\tau \times \ln (0.5))/(\ln [1 - 1/R])$, where $\tau$ is the 6-hour dosing interval and $R$ is the accumulation ratio based on AUC data or the $C_{\text{en}}$ ratio, as defined above.

The amount of meropenem or ICI 213,689 excreted into the urine during each collection interval was calculated as the product of urine concentration and urine volume for that interval. The cumulative urinary recovery over the dosing interval was determined by summing the amounts excreted during each interval. Urinary recovery of meropenem on day 2 only was expressed as a percentage of the administered dose. The recovery of ICI 213,689 on day 2 was expressed as a percentage of the molecular-weight difference between meropenem and ICI 213,689. The renal clearance ($C_{\text{r}}$) of meropenem was calculated from the ratio of the amount excreted during the dosing interval divided by the AUC$_{(0-6h)}$. The nonrenal clearance ($C_{\text{nr}}$) was the difference between the $C_{\text{r}}$ and the $C_{\text{nr}}$.

Statistical analysis. Results were calculated as the group mean with SE (SE was an estimate of variability). An analysis of covariance designed to evaluate a study with a matched-pairs design was performed to compare differences between the two study groups with respect to vital signs and laboratory data. Pharmacokinetic parameters for controls and cases were compared by means of methods appropriate for a matched-pairs study design. Paired *t* tests were performed to assess changes from baseline for each group.

Results

Patient demographics. Eight subjects with hepatic disease (cases) and eight matched subjects without hepatic disease (controls) completed the trial. Seven subjects in each group were male; one subject in each group was female. All cases had cirrhosis of the liver, the diagnosis of which was confirmed by biopsy and a history of alcohol and/or drug abuse. The subjects were clinically stable and did not have ascites, signs of encephalopathy, or bleeding abnormalities. The results of the liver function tests indicated the absence of active hepatic disease. Subjects refrained from the consumption of alcohol from 7 days before study entry until completion of the study. No subject withdrew from the trial prematurely.

Meropenem and ICI 213,689 pharmacokinetics. The mean (SE) values for plasma pharmacokinetic parameters for cases and controls are presented in table 2. Certain data for several controls were unobtainable. The $t_{1/2}$ for one control on study day 2 could not be adequately defined, and, consequently, AUC$_{(0-6h)}$, $C_{\text{r}}$, AUC$_{\text{nr}}$, and $V_{\text{ss}}$ were not derived. Quantifiable plasma concentrations of meropenem for three controls on study day 2 and for one control on study day 4 could not be obtained; therefore, $R$ values could not be calculated. No statistically significant differences in any of these parameters between the first dose and steady state or between groups were found.

The mean plasma meropenem concentration–time profiles on days 2 and 4 for the cases and controls are shown in figure 1. The mean (SE) values for plasma pharmacokinetic parameters of ICI 213,689 for cases and controls are presented in table 3, and the mean plasma ICI 213,689 concentration–time profiles on days 2 and 4 for cases and controls are shown in figure 2.

Urinary recovery and clearance of meropenem and ICI 213,689. Mean (SE) urinary recovery and clearance parameters for meropenem and ICI 213,689 are summarized in table 4. For controls, the amounts of meropenem excreted in urine and cleared by the kidneys decreased at steady state when compared with those amounts measured after a single dose. No such differences were observed for cases.

Safety experience. Each of the 16 subjects received a total of six doses of meropenem between study day 2 and study day 4; each subject received a total of 6 g of meropenem. One case also received glipizide (15 mg b.i.d.) for treatment of diabetes mellitus. A total of 11 adverse experiences were reported by
Table 2. Summary of mean (SE) values for plasma meropenem pharmacokinetic parameters for subjects with hepatic disease (cases) and controls.

<table>
<thead>
<tr>
<th>Study day, parameter (unit)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
</tbody>
</table>

Day 2, first dose
- $C_{max}$ (µg/mL) 8 55.0 (3.7) 8 57.0 (3.0)
- $C_{in}$ (µg/mL) 8 1.4 (0.1) 4 2.4 (1.4)
- $t_{1/2}$ (h) 8 1.2 (0.1) 7 1.4 (0.2)
- AUC$_{0-24}$ (µg·h/mL) 8 78.6 (5.2) 7 71.8 (5.6)
- AUC$_{0-4}$ (µg·h/mL) 8 75.5 (4.5) 4 75.1 (6.8)
- $Cl_p$ (mL/min) 8 218.7 (14.6) 7 241.6 (20.3)
- $V_{ss}$ (L) 8 18.8 (1.4) 7 22.2 (3.4)

Day 4, steady state
- $C_{max}$ (µg/mL) 8 51.2 (3.6) 8 54.6 (4.0)
- $C_{in}$ (µg/mL) 8 1.4 (0.1) 7 1.1 (0.2)
- $t_{1/2}$ (h) 8 1.4 (0.1) 8 1.2 (0.1)
- AUC$_{0-6}$ (µg·h/mL) 8 69.2 (4.6) 7 72.6 (4.8)
- $Cl_p$ (mL/min) 8 250.4 (20.5) 7 236.6 (18.0)
- $R$ (AUC ratio) 8 0.9 (0.03) 4 1.0 (0.06)
- $R$ ($C_{in}$ ratio) 8 1.1 (0.11) 4 0.8 (0.19)

Note: AUC = area under the plasma concentration–time curve; $C_{max}$ = highest observed plasma concentration; $C_{in}$ = plasma concentration at 6 hours after dosing; $Cl_p$ = plasma clearance; $R$ = accumulation ratio; $t_{1/2}$ = terminal half-life; $V_{ss}$ = steady-state volume of distribution.

Four subjects during the study. One case reported five adverse events on day 4 (mild pain in the right arm, right hand, neck, and right shoulder and mild nausea), these events were judged to be "possibly" drug related by the investigator. A second case reported mild diarrhea on day 3 followed by mild dizziness on the next day; again, the investigator categorized these events as "possibly" drug related. One control reported mild flatulence on day 3, which was considered to be "probably" unrelated to treatment, and a second control reported moderate asthenia ("possibly" treatment related) and mild back pain ("probably" unrelated to treatment) on day 4.

No clinically significant treatment-related changes were observed in the results of clinical laboratory tests. Although many laboratory test results were abnormal both at baseline and during treatment of cases, such abnormalities were considered to be related to the disease state. For example, the mean ALT values for the cases were 44.8 U/L (normal range, 0–45 U/L) at baseline, 41.8 U/L at day 2, and 45.7 U/L at day 5. Similarly, the mean AST values for the cases were 56.5 U/L (normal range, 0–41 U/L) at baseline, 50.0 U/L at day 2, and 57.9 at day 5. Changes from baseline values for both ALT and AST were statistically significant, but these changes were not considered to be clinically significant. Other changes in laboratory values for both cases and controls remained within normal ranges. Similarly, changes in pulse rate and blood pressure were within normal ranges at all times for cases and controls.

Figure 1. Mean plasma meropenem concentration–time profiles on day 2 (A) and day 4 (B) for subjects with hepatic disease (dashed line) and matched controls (solid line).
Table 3. Summary of mean (SE) values for plasma ICI 213,689 pharmacokinetic parameters for subjects with hepatic disease (cases) and controls.

<table>
<thead>
<tr>
<th>Study day, parameter (unit)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Day 2, first dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu$g/mL)</td>
<td>8</td>
<td>1.9 (0.2)</td>
</tr>
<tr>
<td>$C_{6h}$ ($\mu$g/mL)</td>
<td>8</td>
<td>0.7 (0.1)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>8</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-6h}$ ($\mu$g $\cdot$ h/mL)</td>
<td>8</td>
<td>7.3 (0.9)</td>
</tr>
<tr>
<td>Day 4, steady state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu$g/mL)</td>
<td>8</td>
<td>2.9 (0.2)</td>
</tr>
<tr>
<td>$C_{6h}$ ($\mu$g/mL)</td>
<td>8</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>8</td>
<td>0.5 (0.06)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-6h}$ ($\mu$g $\cdot$ h/mL)</td>
<td>8</td>
<td>10.3 (1.1)</td>
</tr>
<tr>
<td>$R$ ($\text{AUC}$ ratio)</td>
<td>8</td>
<td>1.5 (0.1)</td>
</tr>
<tr>
<td>$R$ ($C_{\text{max}}$ ratio)</td>
<td>8</td>
<td>1.3 (0.1)</td>
</tr>
<tr>
<td>$t_{\frac{1}{2, \text{eff}}}$</td>
<td>8</td>
<td>3.7 (0.5)</td>
</tr>
</tbody>
</table>

NOTE. AUC = area under the plasma concentration–time curve; $C_{\text{max}}$ = highest observed plasma concentration; $C_{6h}$ = plasma concentration at 6 hours after dosing; $R$ = accumulation ratio; $T_{\text{max}}$ = time to maximum plasma concentration; $t_{\frac{1}{2, \text{eff}}}$ = effective half life.

Discussion

The plasma pharmacokinetic parameters of meropenem for cases and controls were not significantly different ($P = .09$ to .99) when results were compared after single or multiple doses. After single doses, there was a decrease the amount of meropenem excreted in the urine ($P = .038$), a decrease in the $Cl_r$ of meropenem ($P = .011$), and an increase in the $Cl_{\text{ur}}$ of meropenem at steady state ($P = .015$) for cases compared with controls. The reasons for these differences in urinary recovery and $Cl$ are not clear. This finding could be the result of incomplete urine collections and the smaller number of subjects used in the calculation of single-dose clearances. No such differences ($P = .33$ to .93) were observed in the urine-derived parameters for cases.

There were no statistically significant differences in any of the measured or calculated plasma pharmacokinetic parameters of the metabolite ICI 213,689 for cases and controls when results were compared after single or multiple doses ($P = .42$ to .65) or after single doses or steady state ($P = .19$ to .80). The $t_{\frac{1}{2, \text{eff}}}$ of ICI 213,689 was $\sim3.7$ hours for both cases and controls. The mean total urinary recoveries of meropenem plus its metabolite over the first dosing interval were $\sim72\%$ for cases and $82\%$ for controls; these values were not significantly different ($P = .13$).

The findings of this study are consistent with those of previously published reports [1-4, 6-13]. Meropenem is excreted primarily in the urine. More than 65\% of the drug is recovered unchanged in urine, while $\sim20\%$ of the dose is recovered as the microbiologically inactive metabolite ICI 213,689 in subjects with

Figure 2. Mean plasma ICI 213,689 concentration–time profiles on day 2 (A) and day 4 (B) for subjects with hepatic disease (dashed line) and matched controls (solid line).
Table 4. Summary of mean (SE) values for urinary recovery and clearance parameters for meropenem and its metabolite ICI 213,689 for subjects with hepatic disease (cases) and controls.

<table>
<thead>
<tr>
<th>Study day, parameter (unit)</th>
<th>Meropenem</th>
<th>ICI 213,689*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>No. Mean (SE)</td>
<td>No. Mean (SE)</td>
</tr>
<tr>
<td>Day 2, first dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug recovered (%)</td>
<td>8 56.0 (4.2)</td>
<td>8 63.9 (4.5)</td>
</tr>
<tr>
<td>Ae(o-6h) (mg)</td>
<td>8 559.8 (42.4)</td>
<td>8 638.8 (45.2)</td>
</tr>
<tr>
<td>Cl (mL/min)</td>
<td>8 128.6 (15.1)</td>
<td>4 165.5 (17.8)</td>
</tr>
<tr>
<td>Clw (mL/min)</td>
<td>8 90.1 (9.0)</td>
<td>4 48.7 (8.9)</td>
</tr>
<tr>
<td>Day 4, steady state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ae(o-6h) (mg)</td>
<td>8 564.7 (58.2)</td>
<td>8 469.9 (28.6)</td>
</tr>
<tr>
<td>Cl (mL/min)</td>
<td>8 146.1 (22.8)</td>
<td>7 108.6 (11.5)</td>
</tr>
<tr>
<td>Clw (mL/min)</td>
<td>8 104.2 (10.0)</td>
<td>7 127.9 (13.4)</td>
</tr>
</tbody>
</table>

NOTE. Ae = cumulative urinary recovery; Cl = renal clearance; Clw = nonrenal clearance.

* ICI 213,689 is expressed as equivalents of meropenem.

normal renal function [1–4, 9, 10, 12]. The high rate of recovery
of unchanged meropenem in urine, together with evidence that
the major metabolite ICI 213,689 is formed in the kidney [2],
suggests that this agent is not actively metabolized by the liver.
The urinary recovery profile for meropenem is quite similar to
that for imipenem when imipenem is given with cilastatin to
prevent degradation by dihydropeptidase-1 [2].

Liver disease is well known to have an extraordinarily vari-
able spectrum, from well-compensated cirrhosis to grossly un-
compensated disease, and various types of liver disease have
different effects on the activities of hepatic microsomal en-
zymes. Unfortunately, there is no reliable method of quantify-
ing the degree of hepatic impairment that yields relevant data
for pharmacokinetic analysis. Our approach was to conduct a
trial with subjects with clinical liver dysfunction as well as
impairment of hepatic metabolic capacity.

Results from trials in which antipyrine was used as a marker
for drug metabolic activity suggest that subjects with biopsy-
proven alcoholic cirrhosis clearly have reduced drug metabolic
activity when compared with healthy subjects [14]. However,
it has also been found that indicators of either hepatic injury
(i.e., serum bilirubin, transaminases, and alkaline phosphatase)
or hepatic synthetic function (i.e., plasma albumin and pro-
thrombin time) are not useful in predicting impaired hepatic
clearance of drugs.

For example, the clearance of antipyrine in patients with
hepatitis or fatty liver is generally similar to that seen in healthy
subjects. Of course, most drugs cannot be expected to behave
quantitatively like antipyrine because their pharmacokinetic
profiles differ so widely. As the patient population with biopsy-
proven alcoholic cirrhosis appears to be the group most likely
to have reduced drug metabolic capacity, the negative results
observed for that group in this trial may indicate that other types
of liver disease also have no effect on the pharmacokinetics of
meropenem.

Conclusions

Repeated intravenous 1-g doses of meropenem every 6 hours
were well tolerated when administered to healthy controls as
well as to subjects with stable alcoholic cirrhosis. There were
no differences between controls and subjects with hepatic im-
pairment in terms of the pharmacokinetic parameters of either
meropenem or its metabolite ICI 213,689. Therefore, dosage
adjustment of meropenem is not indicated for patients with
alcoholic cirrhosis.

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