AstraZeneca Marketing Company Study Synopsis

Finished product: MERREM™ I.V

Active ingredient: Meropenem
Study Code: 3591IL/0091

An Open-label Study to Determine the Concentration of Meropenem in Plasma and Cantharidin-induced Skin Blister Fluid Following Repeated Intravenous Infusion of Meropenem 500 mg Every 8 Hours in Healthy Males

Publications: Published Study

Status: COMPLETED

Development Phase: 3

First subject recruited: 12/27/2001

Last subject completed: 01/20/2002

Approval date: 05/01/2003

Status (Completed or Ongoing): COMPLETED

Objectives:

To determine the meropenem concentrations in plasma and cantharidin-induced skin blister fluid after repeated intravenous (iv) infusion of 500 mg meropenem every 8 hours (q8h).

Study design:
This was a single-center, multiple-dose, open-label study that planned to enroll at least 8 fully evaluable healthy men. Meropenem (500 mg) was administered by iv infusion over 30 minutes q8h for a total of 3 doses. Twelve to 18 hours before the 3rd dose of meropenem, each subject had 3 separate drops of cantharidin-containing ointment placed on the anterior aspect of each forearm to induce a total of 6 blisters. Fluid from the cantharidin-induced skin blister and blood samples were obtained just prior to and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 12 hours after the start of infusion of the 3rd meropenem dose.

Target subject population and sample size:
Up to 15 healthy men, aged 18 to 45 years, could be enrolled to provide 8 evaluable subjects

Investigational product and comparator(s): dosage, mode of administration and batch numbers:
Meropenem was administered as an iv infusion by means of an infusion pump over approximately 30 minutes q8h for a total of 3 doses. AstraZeneca provided

meropenem in 500-mg/100-ml iv infusion vials (Lot number 2000027129, Formulation (F) number F-12260).

Cantharidin ointment contained 0.2% to 0.3% cantharidin by weight. Cantharidin was prepared for topical application by wetting pure powder (Sigma Chemical, St Louis, MO) with Glycerin U.S.P. and then mixing with an ointment (Anhydrous Ointment, Professional Compounding Centers of America, Inc., Houston, Texas).

Duration of treatment:
A total of 3 doses of meropenem were administered starting in the evening of Day 1 and completing on Day 2.

Key eligibility criteria:
Subjects had to fulfill the following: give written informed consent and comply with the requirements of the study, have creatinine clearance values within normal age-adjusted range as estimated by the Cockcroft-Gault clearance equation, and have negative results of urine screen for drugs of abuse including nicotine. In addition, subjects had to have no history or suspected hypersensitivity to cephalosporins, penicillins, or carbapenems; no seizure disorders; no clinically significant deviations in physical examinations, vital signs measurements, or clinical laboratory tests results; and no use of any anti-infective within 30 days before study entry.

Pharmacokinetics:
The primary variable was concentration of meropenem in skin blister fluid and in plasma after repeated iv infusion of 500 mg meropenem q8h.

Safety:
Safety assessments included the following: reports of adverse events, subjective symptoms, clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs measurements before and after each iv infusion, and physical examinations.

Statistical methods:
All pharmacokinetic parameters were summarized descriptively. Summaries of safety measures were provided. Adverse events were summarized for all subjects by body system and preferred term. Clinically significant laboratory abnormalities were discussed.

Subject population:
Ten subjects received meropenem treatment.

Table S1 Subject population and disposition:

| | Meropenem |
|---|---|

| | | |
|---|---|---|
| Population | | |
| Number treated | | 10 |
| | | |
| Demographic characteristics | | |
| Sex, number (%) of subjects | Male | 10 (100) |
| | Female | 0 |
| Age (years) | Mean (SD) | 26.7 (5.9) |
| | Range | 21 to 42 |
| Race, number (%) of subject | Caucasian | 7 (70) |
| | Black | 0 |
| | Asian | 0 |
| | Hispanic | 1 (10) |
| | Other | 2 (20) |
| Disposition | | |
| Number (%) of subjects who | Completed | 9 (90) |
| | Discontinued | 1 (10) |
| Number analyzed for safety | | 10 |
| Number analyzed for pharmacokinetics | | 9 |

Pharmacokinetic results:
Nine healthy men were evaluable for pharmacokinetics. After a 30-minute iv infusion, meropenem (500 mg q8h) distributed well into cantharidin-induced skin blister fluid. The mean percent penetration based on the blister fluid AUC(0-8)/plasma AUC(0-8) plasma ratio was 66% (range 43% to 95%). The elimination half-life of meropenem in blister fluid (mean 1.83 hours; range 1.41 to 2.47) was longer than that observed in plasma (mean 0.96 hours; range 0.71 to 1.46 hours). Although initially lower than the mean plasma meropenem concentration, the mean skin blister concentration was 3.42 mg/ml (range 2.26 to 5.37 mg/ml) at 3 hours after the start (at 38% of the dosing interval) at which time it exceeded and continued to exceed the mean plasma levels.

Table S2 Mean (SD) pharmacokinetic parameters for a 30-minute infusion of 500 mg meropenem q8h, following the 3rd dose

| Parameter | Mean (SD) | Range |
|---|---|---|
| Plasma (N=9) | | |
| Cmax, mg/ml | 24.02 (4.26) | 19.7 to 32.8 |
| tmax, h | 0.51 (0.02) | 0.50 to 0.55 |
| t1/2, h | 0.96 (0.25) | 0.71 to 1.46 |
| AUC(0-8), mgúh/ml | 28.61 (4.84) | 23.49 to 39.18 |
| CL, L/h | 17.88 (2.59) | 12.80 to 21.30 |
| Vdss, L | 25.59 (4.21) | 17.50 to 32.10 |
| Skin blister fluid (N=9) | | |

| | | |
|---|---|---|
| Cmax, mg/ml | 5.48 (1.91) | 3.21 to 8.58 |
| tmax, h | 1.22 (0.64) | 0.57 to 2.03 |
| t1/2, h | 1.83 (0.36) | 1.41 to 2.47 |
| AUC(0-8), □g.h/ml | 18.92 (5.68) | 11.57 to 31.36 |
| % Penetration[a] | 66 (18) | 43 to 95 |

a Defined as the ratio of blister fluid AUC(0-8)/plasma AUC(0-8).
SD Standard deviation. N Total number of subjects. AUC(0-8) Area under the concentration time curve from zero to time t [amount .time/volume].
Cmax Peak concentration. Vdss Volume of distribution at steady state. CL Total clearance of drug from plasma [volume/time].
Tmax Time to maximum concentration. t
Elimination half-life.

Safety results:
Safety results are summarized in Tables S3 and S4.

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

| Category of adverse event | Number (%) of subjects who had an adverse event in each category[a] |
|---|---|
| | Meropenem (Total number of subjects = 10) |
| Any adverse events | 4 (40) |
| Serious adverse events | 0 |
| Withdrawals due to adverse events | 1 (10) |
| Treatment-related adverse events | 2 (20) |
| | Total number of adverse events[b] |
| Adverse events[b] | 8 |
| Serious adverse events[b] | 0 |
| Adverse events that led to withdrawal[b] | 5 |
| Treatment-related adverse events[b] | 6 |

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted
b Events are counted by preferred term, ie, for a subject with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

Table S4 Number (%) of subjects with adverse events (safety population)

| System organ class | Preferred term (COSTART) | Number (%) of subjects with adverse events |
|---|---|---|
| Whole body | Headache | 2 (20) |
| | Fever | 1 (10) |
| | Digestive Diarrhea | 1 (10) |
| | Nausea | 1 (10) |
| | Vomiting | 1 (10) |
| Metabolic and nutritional | Bilirubinemia | 1 (10) |
| | Dehydration | 1 (10) |

Meropenem was well tolerated. No serious adverse events occurred. Only 1 subject was withdrawn from the trial; the withdrawal involved multiple adverse events (diarrhea, vomiting, nausea, dehydration, and fever) possibly associated with a viral stomach illness or possibly related to study medication. Bilirubinemia occurred in another subject on Day 3 but a repeat total bilirubin test on the same day was normal (repeat value was lower than the baseline result).