SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Ceftobiprole medocaril
Name of Active Ingredient(s)	Ceftobiprole

Protocol No.: CEFTOCSI1008

Title of Study: Open-Label, Single Dose, Parallel Group Pharmacokinetic Study of Ceftobiprole in Morbidly Obese and Non-Obese Subjects

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Publication (Reference): None

Study Period: 02 October 2007 to 14 November 2007

Phase of Development: Phase 1

Objectives: The primary objective was to compare the pharmacokinetics of ceftobiprole in morbidly obese subjects and non-obese subjects. The secondary objectives were to assess the pharmacodynamics as defined by the percent time above MIC (%T>MIC) and to assess safety and tolerability of ceftobiprole in order to support dosing recommendations in the morbidly obese population.

Methods: This was an open-label, single center, parallel-group Phase 1 study in morbidly obese and non-obese men and women. A total of 25 subjects (12 morbidly obese and 13 non-obese subjects) were enrolled in the study. There were 4 phases in the clinical study: the pretreatment (screening/baseline) phase of up to 21 days; the 2-day open-label treatment phase when each subject received a single 2-hour infusion of ceftobiprole 500 mg followed by 24 hours of blood and urine sampling; the end-of-study phase; and the follow-up phase of approximately 1 week after the last pharmacokinetic sample when each subject was monitored by telephone for development of new adverse events and assessment of ongoing adverse events.

Diagnosis and Main Criteria for Inclusion: Healthy men and women between 19 and 55 years of age, inclusive. Morbidly obese subjects had BMI of $\geq$40 kg/m^2. Morbidly obese subjects with controlled hypertension who were not taking diuretics were included in the study. Non-obese subjects had a BMI between 18 and 30 kg/m², inclusive and a body weight not less than 50 kg. Morbidly obese and non-obese subjects were matched individually 1:1 by age (±10 years), sex, and creatinine clearance (±20%). Subjects were non-smokers in overall good health with normal renal function based on creatinine clearance calculated by the Cockroft-Gault equation adjusted for ideal body weight. Subjects with a history of urinary obstruction or difficulty in voiding and women pregnant or breast-feeding were excluded.

Test Product, Dose and Mode of Administration, Batch No.: Ceftobiprole 500 mg (ceftobiprole medocaril) (lot No. IO30603) was administered intravenously over a 2-hour infusion.

Duration of Treatment: up to 30 days (up to 21 days screening plus 2 days open-label treatment phase plus 1-week follow-up).

Criteria for Evaluation:

Pharmacokinetics: Based on individual plasma and urine concentration-time data, the following pharmacokinetic parameters of ceftobiprole and the open-ring metabolite in plasma and urine were estimated: f_u (ceftobiprole only), C_{max}, t_{max}, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2}$, CL (ceftobiprole only), Vd_z (ceftobiprole only), CL_R, Ae, %Dose and CL_{CR}. Pharmacokinetic parameters in plasma and urine were calculated using noncompartmental pharmacokinetic analysis (NCA) with WinNonlin Version 5.2.

Pharmacodynamics: Time above the targeted MIC of 4 μg/mL (T>MIC) and the percent time above MIC (%T>MIC) for total and free ceftobiprole were calculated assuming 8-hour using WinNonlin Version 5.2. Free ceftobiprole was calculated based on the measured protein binding of ceftobiprole in plasma.

In addition to pharmacodynamic analysis planned in the protocol, T>MIC and %T>MIC assuming 12-hour dosing intervals were estimated for total and free ceftobiprole concentrations using WinNonlin Version 5.2.

Safety: Safety and tolerability were evaluated throughout the study. Safety from Day -1 through the post-study follow-up were evaluated by examining incidence, severity, relationship to study drug, and type of adverse events, changes in clinical laboratory results, physical examination and vital signs measurements as well as concomitant therapy.

Statistical Methods: Pharmacokinetic parameters (AUCs and C_{max}) of ceftobiprole for morbidly obese subjects and non-obese subjects were compared using 90% confidence intervals for the ratio of mean pharmacokinetic parameters. Analysis of variance models were fit to the logarithm of the selected pharmacokinetic parameters data from morbidly obese subjects and non-obese subjects, with group (morbidly obese, non-obese) as a factor. Using the least squares means and inter-subject standard deviation from the model, the estimated difference in means and 90% confidence intervals for the difference in means on log-scale were obtained for morbidly obese subjects versus non-obese subjects. The results were back-transformed using antilogarithm to obtain the estimated ratio of mean pharmacokinetic parameters and 90% confidence intervals for the ratio of means. Additional graphical presentations of selected pharmacokinetic parameters (CL, Vd_z, and $t_{1/2}$) versus body weight and BMI were explored. Free ceftobiprole calculated based on the measured protein binding of ceftobiprole in plasma in each subject group was summarized and compared with results from previous studies.

RESULTS:

A total of 25 subjects, 12 morbidly obese (8 women and 4 men) and 13 demographically matched non-obese subjects (9 women and 4 men), between 19 and 55 years of age were enrolled in the study. Ten of the morbidly obese subjects and all 13 non-obese subjects were white and 2 morbidly obese subjects were African-American. The mean weight and body mass index were 130.9 kg and 45.5 kg/m^2 for morbidly obese subjects and 73.5 kg and 24 kg/m^2 for non-obese subjects, respectively. A total of 12 morbidly obese and 12 non-obese subjects completed the study. One non-obese subject withdrew consent before the completion of the study, after the 8-h sample collection and was excluded from pharmacokinetics and statistical analysis (except for the calculation of C_{max} and t_{max}). One morbidly obese subject who completed the study displayed a plasma concentration profile of ceftobiprole, which was inconsistent with the 2-hour infusion administration and was excluded from the pharmacokinetic analysis. No protocol deviations were recorded for this subject. All 25 subjects were included in the safety analysis.

<u>PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:</u>

Mean (SD) ceftobiprole plasma pharmacokinetic parameters following a single 2-hour intravenous infusion of ceftobiprole 500 mg in morbidly obese and non-obese subjects are summarized in the next table.

Summary of Plasma Ceftobiprole Pharmacokinetic Parameters

Pharmacokinetic Parameters	Morbidly Obese 500 mg 2-h infusion. (N=11)[c]	Non-Obese 500 mg 2-h infusion. (N=13)
AUC_{last} (µg•hr/mL)	90.5 (11.6)	109 (20.0)[a]
AUC_{∞} (µg•hr/mL)	91.0 (11.7)	110 (20.1)[a]
C_{max} (µg/mL)	21.4 (2.99)	30.2 (4.32)
t_{max} (hr)[b]	1.90 (1.67-2.17)	1.98 (1.67-2.02)
$t_{1/2}$ (hr)	3.38 (0.258)	3.21 (0.472)[a]
CL (L/hr)	5.58 (0.745)	4.65 (0.652)[a]
Vd_z (L)	27.2 (3.91)	21.6 (5.09)[a]
f_u (%)	86.0 (4.29)[d]	84.4 (3.96)

[a] N= 12

[b] Median (Min-Max)

[c] Subject 100801 displayed plasma ceftobiprole concentration profile over the 2-hour infusion period inconsistent with dosing information. Since no protocol deviation was recorded for this subject, the source of the unexpected plasma concentration profile during the infusion period remains unknown. Subject 100801 was excluded from descriptive statistics of pharmacokinetic parameters for morbidly obese subjects.

[d] N=9

Overall, the mean systemic exposure (AUC) and peak concentration (Cmax) of ceftobiprole in morbidly obese subjects were approximately 17% and 29% lower than that observed in non-obese subjects. The mean volume of distribution in morbidly obese subjects was 26% higher than that observed in non-obese subjects. Half-life, clearance, volume of distribution and free fraction of plasma ceftobiprole in non-obese subjects were consistent with those previously published in the literature. Log-transformed pharmacokinetic parameters ($AUC_{last,}$ AUC_{∞} and C_{max}) of ceftobiprole in morbidly obese versus non-obese subjects were compared using an ANOVA model. Overall, 90% confidence intervals of ratios of geometric means for AUC and C_{max} ranged from 75% to 92% and 64% to 78%, respectively.

Individual clearance and volume of distribution values of ceftobiprole were graphically correlated to body weight of morbidly obese and non-obese subjects. A positive correlation was observed between the clearance and volume of distribution of ceftobiprole and the body weight and BMI in morbidly obese and non-obese subjects. For morbidly obese and non-obese subjects, approximately 83% and 87%, respectively, of the dose was recovered in urine as unchanged ceftobiprole.

The systemic exposure of the open-ring metabolite was approximately 90% lower than ceftobiprole in both populations. For morbidly obese and non-obese subjects, approximately 6% and 8%, respectively, of the ceftobiprole dose was recovered in urine as the open-ring metabolite. The total urinary recovery of the administered 500 mg dose as the sum of the parent and metabolite was approximately 89% in morbidly obese and 95% in non-obese subjects.

Concentrations of total ceftobiprole in morbidly obese and non-obese subjects were above the targeted MIC (4 µg/mL) 84.0% and 86.8% of the time, respectively, over an 8-hour dosing interval and 56.4% and 59.8 % of the time, respectively, over a 12-hour dosing interval. Free ceftobiprole concentration values were above the MIC in morbidly obese and non-obese subjects 76.6% and 79.7% of the time, respectively, over an 8-hour dosing interval and 51.2% and 54.3% of the time, respectively, over a 12-hour dosing interval.

SAFETY RESULTS:

No deaths or other serious adverse events were reported in the current study, and no subject discontinued treatment because of an adverse event. Overall, a total of 10 mild or moderate adverse events were reported (3 in the non-obese group and 7 in the morbidly obese group). Dysgeusia (taste impairment) was the most frequent adverse event in morbidly obese subjects, while headache occurred in similar frequency in both morbidly obese and non-obese subjects. Two subjects (1 subject in the morbidly obese group and 1 subject in the non-obese group) reported pain or tenderness at the infusion site. One non-obese subject reported gastrointestinal disorders (nausea, retching and vomiting). Two subjects reported hematoma. The investigator considered the reports of pain at the infusion site as very likely related to the study drug. Reports of dysgeusia and tenderness at the infusion site were considered as probably related to the study drug. Reports of headache and gastrointestinal symptoms were considered as possibly related to the study drug. The hematoma was considered to be of doubtful relationship or not related to study drug. All adverse events were either mild or moderate in severity; no adverse event was considered severe. No adverse events persisted at the end of the study.

There were no clinically noteworthy out-of-range clinical laboratory values or changes in clinical laboratory values from screening to the end of study/early withdrawal visit. There were no other clinically noteworthy changes in vital sign measurements from screening to the end of study/early withdrawal visit.

CONCLUSION:

Following a single 500 mg 2-hour intravenous infusion, ceftobiprole pharmacokinetic differences were characterized by an increased volume of distribution and clearance, resulting in an approximately 17% lower exposure, among morbidly obese compared with non-obese subjects.

The comparable %T>MIC in morbidly obese and non-obese subjects suggests that no dose adjustments should be required in morbidly obese subjects based on body mass index alone.

Ceftobiprole 500 mg administered as a single 2 hour infusion was safe and well tolerated in both morbidly obese and non-obese subjects.

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