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TEICOPLANIN ("TARGOCID"; MERRELL DOW PHARMACEUTICALS AUSTRALIA PTY LTD) POWDER FOR INJECTION IN VIALS 100, 200 AND 400 mg PLUS WATER FOR INJECTION

TGA File number 86/9010

GENERAL MARKETING APPLICATION

EVALUATION OF A BIOAVAILABILITY STUDY COMPARING INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION

Investigators: G.Thompson, K.Antony, L.Yuh, H.Boxenbaum, I.Rios, P.Schechter, E.Lewis, R.Kuzma, M.Eller, W.Louv, R.Okerholm

Study site: Departments of Drug Metabolism, Biostatistics and Antibiotics/Anti-infectives of the Merrell Dow Research Institute, Cincinnati, Ohio, USA.

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Evaluator: [redacted]
Department of Clinical and Experimental Pharmacology
Medical School North,
University of Adelaide
Frome Road
Adelaide 5000

Signed: [redacted]

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This evaluation has been based on the information provided by the company in its submission dated March, 1991.

INTRODUCTION

The general marketing application is for the marketing of teicoplanin in a preparation designed for parenteral administration. Although the primary route of administration is expected to be intravenous, the company has also investigated the possibility of intramuscular dosing and to this end has provided data comparing the bioavailability of teicoplanin by the two routes. The same preparation was administered by both routes and was identical to the formulation which is the subject of the marketing application.

Two such bioavailability studies have been supplied in the present B1 submission, one dated April 1984 which included 6 subjects, and the other dated January - March 1989 which included 24 subjects. In the accompanying letter from the company, it is stated that the more recent study was undertaken in order to correct some deficiencies in the presentation of the original study. The 1990 study is therefore the subject of this evaluation, although it should be noted that the major conclusions of the two studies are very similar (the original study having shown the relative bioavailability of IM route to be about 90% compared with IV).

Quality control data are provided for the formulation used in the study (presented as 400mg per 3 mls vial in normal saline). The data demonstrate that the assayed content of teicoplanin was satisfactory. Because of the nature of the formulation, dissolution rates were not applicable. The batch number was IC-4068, and the formulation is supplied.

The study report was signed by the investigators. There is also a statement that all data were generated under the supervision of the investigators, and each case record contained a statement that the data were checked by at least one investigator in addition to the person who originally generated the data.

SUBJECTS

The study was carried out in 24 healthy male volunteers aged from 18 to 47 years (median 26) and all were within 10% of normal weight for height. One subject was withdrawn after the first phase because of concurrent medication for a headache and was not replaced. Inclusion and exclusion criteria (included in protocol, appendix A p 0049A) were appropriate, as were the clinical and laboratory evaluation.

The ingestion of any medication within 5 days prior to the start of the study was prohibited. The drug was administered while the subjects were in the supine position and they were required to remain in this position for one hour after the intravenous infusion. Subjects were fasted overnight for ten hours and received a standard breakfast one hour before dosing. Subsequent meals were also standardized. The ingestion of alcohol was prohibited throughout the dosing and collection period.

ETHICAL CONSIDERATIONS

All subjects provided written informed consent of a form previously approved by an Institutional Review Board prior to entry into the study. A copy of the form is not included in the report and therefore has not been evaluated. Written evidence of IRB approval has not been provided, although there is a statement that "clinical studies concerned with the development of teicoplanin for the treatment of Gram-positive infections were conducted in conformance with the Declaration of Helsinki". In addition, it is stated that a copy of the written approval was submitted to Merrell Dow Research Institute prior to the start of the study.

STUDY DESIGN

The 24 subjects were randomized to receive teicoplanin by the intravenous and intramuscular routes in a double-blind fashion (normal saline being given by the alternative route in each phase). Blood and urine samples were collected for 21 days following administration of a single dose of 6 mg/kg and there was an additional week to allow washout between the two phases. Subjects were studied in three groups of eight on successive days in both phases.

The drug was administered either as an intravenous infusion over 30 minutes or as a deep intramuscular injection. Subjects were confined to the study centre from the evening prior to dosing until after the collection of the 21 day samples in each treatment period. All meals were standardized throughout the collection period.

Blood samples were obtained at 0, 30, 35, 45, 60 minutes and 2, 3, 4, 5, 6, 8, 12, 24, 36 and 48 hours after the start of the intravenous infusion, followed by additional blood samples every 24 hours for a further 19 days. Urine was pooled every 24 hours for 21 days from the start of the intravenous infusion. Given previous reports of a T_{max} of about 4 hours after intramuscular administration and a terminal elimination half-life of 50 - 150 hours, the sampling schedule was appropriate. Actual sampling times are included in the report and were very close to the planned times.

The handling of blood and urine samples after collection is described in the protocol (page 0056) and was satisfactory. Stability of teicoplanin in serum and urine was checked and found to be satisfactory over the period of storage.

ANALYTICAL METHODS

The concentration of teicoplanin in serum and urine was determined using a microbiological assay method which has been evaluated by Dr M.Smith of the Antibiotics Section, TGA Laboratories, and found to be acceptable.

In brief, the assay was performed by a petri-dish diffusion technique, the test organism being *Bacillus subtilis*. The standard curve covered the concentration range 0.25 to 32 micrograms/ml of teicoplanin and samples were diluted as required prior to assay. The coefficient of variation of the assay was less than 10% at all concentrations, including the lower limit of quantitation (0.257 mg/L for serum and 0.76 mg/L for urine). In addition,

the mean accuracy was within 6% (for serum) or 10% (for urine) of spiked concentrations at all concentrations including the lower limit of quantitation.

Validation data for the assay have been described in Dr Smith's report on behalf of the TGA Laboratories.

BIOAVAILABILITY ASSESSMENT

The individual values of C_{max} and T_{max} were determined from the raw data. The area under the concentration-time curve, $AUC_{0\text{-last}}$ was determined from t=0 to the last measurable concentration point (up to 504 hours) by the linear trapezoidal rule. The area under the curve extrapolated to infinity, $AUC_{0\text{-inf}}$, was determined by calculating $AUC_{0\text{-last}}$ and adding the estimated residual area, calculated by dividing the last concentration point (C_{last}) by the elimination rate constant, k.

The elimination rate constant was estimated by log-linear regression of the terminal elimination phase for each subject, using the method of least squares regression and based on an adequate number of data points (at least 6) for each subject. The terminal elimination half-life was obtained as 0.693/k. It should be noted that in the calculations in the submission, data points with values as low as 0.19 mg/L were included (0.19 mg/L being quoted as the lower limit of quantitation), despite the limit of 0.257 mg/L quoted in the assay validation section. However, inspection of the data reveals that the calculation of the elimination rate constant did not depend critically on these values and that there was no significant effect on the reported results.

The bioavailability assessment seems adequate and reliable. This was confirmed by recalculation of some of the data sets:

Subj	Route	parameter	reported	recalc	ratio%
#1	IV	$AUC_{0\text{-inf}}$	398.2	398.2	100
		$t_{1/2}$	147.9	147.9	100
#2	IM	$AUC_{0\text{-inf}}$	637.9	637.9	100
		$t_{1/2}$	181.5	181.4	100
#13	IM	$AUC_{0\text{-inf}}$	587.7	587.7	100
		$t_{1/2}$	168.0	167.9	100
#14	IM	$AUC_{0\text{-inf}}$	690.5	690.5	100
		$t_{1/2}$	190.9	190.9	100
#22	IV	$AUC_{0\text{-inf}}$	540.5	540.4	100
		$t_{1/2}$	185.7	185.6	100

Note: units for AUC: mg.hr/L; units for $t_{1/2}$: hours.

All of the recalculated values differed by less than 1% from the values in the report. The pharmacokinetic parameters presented in the report are therefore considered to be accurate.

The following statistical methods were used (following log transformation if the distribution of the data was non-normal):
- ANOVA and the resulting 90% confidence intervals of the ratio of IM:IV administration, except for T_{max} and C_{max}.
- summary statistics were generated for C_{max} and T_{max}.

RESULTS

The mean concentration-time curves (but without standard deviations) are shown in Figure 1. The mean values of the estimated pharmacokinetic parameters and the calculated confidence intervals of the ratio (IM:IV) are presented below. Standard deviations are shown in parentheses.

	IM	IV	mean ratio% 95%CI IM/IV
$AUC_{0\text{-}inf}$ (mg.h/L)	644.7 (100.4)	575.9 (86.3)	111.9% (107.6,116.3)
C_{max} (mg/L)	12.9 (5.9)	46.3 (12.02)	note 1
T_{max} (hr)	4.1 (1.2)	0.51 (0.02)	note 1
$t_{1/2}$ (hr)	198.9 (48.7)	177.9 (40.5)	111.2% (102.1,120.3)

Note 1: since C_{max} and T_{max} after intravenous infusion depends on the rate and duration of the infusion, comparison with results for intramuscular injection was not made.

Inspection of the individual subject results reveals that the range of ratios of extrapolated AUC (IM:IV) was 0.96 to 1.43. The individuals with the highest ratios were subjects numbers 7 and 2. Inspection of the plasma concentrations vs time curves for these subjects suggests possible reasons for the results. In the case of subject #7, the results for IM administration appear questionable, since a large proportion (32.2%) of $AUC_{0\text{-}inf}$ was extrapolated, and the apparent elimination half-life was approximately double the value for the same subject after the IV dose. In the case of subject #2 there is an apparently artifactual data point at 36 hours during the intravenous phase which reduced the AUC for this phase. In general, the individual concentration-time curves show a very similar profile from 6-8 hours after dosing by the two routes.

COMPARISON WITH LITERATURE

Previous pharmacokinetic studies on teicoplanin have been carried out as company studies and the comparison is therefore based on results quoted in the submission.

It is stated in the submission that the intravenous pharmacokinetics of teicoplanin in the current study were similar to the results of a previous study using the same dose. Similarly, in the earlier pharmacokinetic

study described in the Introduction above, the mean AUC_{0-inf} after a single dose of 6 mg/kg was 520.9 mg.h/L, which is similar to the present result of 575.9 mg.h/L. Although the half-life reported in the previous study was only 47 hours, it is likely that this was an underestimate related to an inadequate sampling period of only 102 hours post-dose.

PRODUCT INFORMATION

The draft Product Information which was included for evaluation is satisfactory with the exception of the section on pharmacokinetics, which should be expanded to include a description of the concentration profile after intramuscular injection (peak at about 4 hours; lower C_{max} than after intravenous injection, complete absorption from site of injection).

SUMMARY

The bioavailability study comparing intramuscular with intravenous administration of teicoplanin was well designed and performed according to acceptable standards. On the basis of the present results the intramuscular route of administration is considered bioequivalent with respect to the extent of absorption although having the expected increase in T_{max} and reduction in peak concentration compared with intravenous infusion.

CONCLUSIONS

The proposed use of the intramuscular route of administration for teicoplanin is supported by the results of the present study.

FIGURE1. MEAN TEICOPLANIN SERUM CONCENTRATION TIME PROFILE FOLLOWING SINGLE DOSE IV AND IM ADMINISTRATION OF 6 MG/KG (102-018)