Br. J. clin. Pharmac. (1991), **32**, 255–257

Pharmacokinetics of trospectomycin sulphate in healthy subjects after single intravenous and intramuscular doses

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The pharmacokinetics of trospectomycin (75–1000 mg free base equivalents) were studied in 128 healthy males (eight per dose group), after a 20 min intravenous (i.v.) infusion and intramuscular (i.m.) injection of trospectomycin sulphate. The concentrations of trospectomycin in serum were described by bi- or tri-exponential disposition functions indicating an initial half-life of 1.1–1.4 h for the i.v. dose and 1.6–2.1 h for the i.m. dose and terminal half-lives of over 15 h. Most of the drug was eliminated rapidly (mean residence time 5–12 h). The distribution volume was 59–112% of body weight and clearance was 112–152 ml min^{-1}. The absorption into blood after i.m. dosing was rapid. The area under the concentration-time curve and maximum concentration values were linearly related to dose. Serum drug concentrations fell below the minimum inhibitory concentration values for a variety of organisms by 8–12 h, which indicates that two or three times daily dosing would be appropriate. However, the long terminal half-life suggests that significant accumulation is likely in some tissues with an 8 h dose interval and this may prolong the action of trospectomycin.

Keywords pharmacokinetics trospectomycin

Introduction

Trospectomycin sulphate (6′ propylspectinomycin sulphate) has *in vitro* activity against a broad spectrum of both gram positive and gram negative aerobic and anaerobic bacteria, as well as against *Chlamydia trachomatis*, and it is 8–10 times more potent than spectinomycin (Zurenko *et al.*, 1988).

Previous pharmacokinetic studies in rats and dogs (Nichols & Bye, 1989) indicated that the disappearance of trospectomycin from plasma could be described by a bi-exponential function with half-lives of 20 min and 60 h in the rat and 30 min and 70 h in the dog. There was no evidence of significant metabolism. A preliminary pharmacokinetic study in healthy volunteers, carried out using a microbiological assay for plasma trospectomycin after single intravenous (i.v.) and intramuscular (i.m.) dosage, indicated a short half-life in plasma of 2 h (Zurenko *et al.*, 1988).

Because the microbiological assay had a sensitivity of only 1 μg ml^{-1}, the concentrations of trospectomycin in plasma were not measureable in man beyond 18 h after injection. With the development of a sensitive (< 0.01 μg ml^{-1}) h.p.l.c. assay (Simmonds *et al.*, 1990) it was possible to re-assay the samples and re-evaluate the pharmacokinetics of trospectomycin in these subjects, to determine whether the disposition of the drug in man is comparable with that in dog and rat. This was relevant to relating the animal toxicology to man since reversible changes in the serum liver enzymes (alanine and aspartate transaminases) appeared to be associated with a prolonged retention of drug in the liver of the animals (Cox *et al.*, 1989, 1990; Ulrich *et al.*, 1990). On the other hand, the persistence of drug in the tissues could be a desirable pharmacokinetic feature in relation to the treatment of intracellular infection. It is not clear whether there is any tissue sequestration in man but a prolonged terminal half-life would suggest this.

Methods

One hundred and twenty-eight healthy male volunteers with normal vital signs and laboratory values were studied. They had no history of allergies to medications, liver or renal disease, no current symptoms, no history of seizure disorder and they were aged between 18 to 55 years and were within 20% of ideal weight. The subjects received no medication for the preceding 2 weeks nor any anti-

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biotics for the preceding 30 days. No alcohol was consumed 48 h prior to the study. The study protocol was reviewed by the Institutional Ethics Committee and all subjects gave written informed consent to participate.

Trospectomycin sulphate dissolved in sterile saline was administered to groups of eight subjects at doses (expressed in free base equivalents) of 75, 150, 300, 450, 600, 750, 900 and 1000 mg (300 mg ml^{-1}) by both i.m. injection and a 20 min i.v. infusion. Blood was withdrawn by venepuncture just before administration and then at 10, 20 and 30 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 and in some cases at 48 and 96 h. Samples were not collected to 96 h in all individuals because at the time of the study it was expected that drug would be undetectable beyond 24 h. Serum drug concentrations were measured by an h.p.l.c. assay with a sensitivity of 10 ng ml^{-1}. Calibration graphs were linear; the correlation coefficient of replicate graphs of seven points in duplicate was 0.9996 with a coefficient of variation for the slope of 3%. Within assay and between assay coefficients of variation at 22 ng ml^{-1} were 5% and 3.7% measured over 13 analytical runs (Simmonds *et al.*, 1990).

Pharmacokinetic analysis

The concentration-time data were fitted by bi- and tri-exponential functions using NONLIN84 (Metzler & Weiner, 1984) with a weighting of 1/(observed concentration)^2. Selection of the best function was based upon Akaike's information criterion, comparison of the coefficients of variation (CV) of the parameter estimates, visual examination of plots of the fitted and actual data and examination of the normality of the distributions of the residuals. The initial ($t_{½\lambda_1}$) and terminal ($t_{½z}$ half-lives were calculated by NONLIN84. Values of AUC, AUMC, CL, MRT and V_{ss} were calculated by non-compartmental methods (Gibaldi & Perrier, 1982). ANOVA, followed by Student Newman Keuls multiple range test, was used to compare the kinetic parameters at different doses (SAS Version 5.18, 1985).

Table 1 Pharmacokinetic parameters (mean ± s.d.) of trospectomycin in healthy subjects after i.v. infusion of drug (n = 7–8)

	Dose (mg)							
	75	*150*	*300*	*450*	*600*	*750*	*900*	*1000*
C_{max} ($\mu g\ ml^{-1}$)	4.51 ± 0.47	9.92 ± 1.60	20.6 ± 3.34	27.5 ± 3.57	39.5 ± 5.21	49.8 ± 6.12	73.7 ± 22.75	73.2 ± 21.27
AUC ($\mu g\ ml^{-1}\ h$)	9.0 ± 1.3	20.0 ± 4.2	42.7 ± 7.9	63.8 ± 14.7	83.7 ± 11.7	115.3 ± 9.2	130.0 ± 24.9	154.5 ± 13.0
CL ($ml\ h^{-1}$)	8557 ± 1444	7863 ± 1981	7186 ± 1047	7392 ± 1703	7281 ± 980	6544 ± 556	7128 ± 1242	6512 ± 558
MRT (h)	7.3 ± 2.1	7.4 ± 1.4	8.6 ± 5.0	7.5 ± 4.6	5.3 ± 1.1	6.5 ± 2.2	5.3 ± 3.1	7.4 ± 1.9
V_{ss} (l)	61.0 ± 21.1	55.9 ± 10.8	62.1 ± 41.8	49.0 ± 18.1	37.2 ± 8.3	41.3 ± 14.1	38.4 ± 28.4	46.7 ± 11.3
$t_{½\lambda_1}$ bi-exp (h)	1.3 ± 0.2	1.4 ± 0.1	1.4 ± 0.1	1.1 ± 0.2	1.2 ± 0.3	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.1
$t_{½z}$ bi-exp (h)	15.1 ± 4.4	18.7 ± 6.4	17.5 ± 9.3	10.0 ± 4.6	6.9 ± 1.5	6.6 ± 1.7	5.9 ± 2.2	9.1 ± 2.2
$t_{½z}$ tri-exp (h)	25.4 ± 7.5	26.2 ± 11.2	27.4 ± 23.9	*	*	*	*	*

Pharmacokinetic parameters (mean ± s.d.) of trospectomycin in healthy subjects after i.m. injection of drug (n = 6–8)

C_{max} ($\mu g\ ml^{-1}$)	3.22 ± 0.56	5.50 ± 0.69	10.18 ± 2.30	14.08 ± 3.93	19.29 ± 2.56	23.76 ± 3.74	25.25 ± 5.62	28.31 ± 5.05
AUC ($\mu g\ ml^{-1}\ h$)	11.3 ± 2.2	20.4 ± 2.6	42.2 ± 4.2	64.8 ± 7.9	82.4 ± 13.5	105.0 ± 10.4	125.0 ± 19.1	140.9 ± 13.4
CL ($ml\ h^{-1}$)	6835 ± 1072	7455 ± 1057	7163 ± 683	7030 ± 821	7459 ± 1277	7213 ± 808	7339 ± 1076	7147 ± 612
MRT (h)	11.7 ± 1.9	8.8 ± 2.9	9.0 ± 2.3	11.7 ± 1.5	11.2 ± 2.7	9.5 ± 2.3	10.8 ± 2.3	8.7 ± 1.6
V_{ss} (l)	78.7 ± 21.2	62.4 ± 20.3	62.6 ± 19.8	79.5 ± 15.9	80.4 ± 25.7	65.4 ± 14.4	74.3 ± 15.4	58.3 ± 12.1
$t_{½\lambda_1}$ (h)	1.7 ± 0.1	1.7 ± 0.2	1.9 ± 0.3	1.8 ± 0.2	1.9 ± 0.4	2.1 ± 0.3	2.0 ± 0.3	1.9 ± 0.1
$t_{½z}$ (h)	32.0 ± 8.3	25.5 ± 9.7	27.1 ± 7.5	35.8 ± 3.5	34.5 ± 9.8	31.0 ± 3.9	31.9 ± 10.1	22.9 ± 5.6

* Parameters for the tri-exponential function are not presented because concentration data was not available beyond 24 h.

Results

Over the dose range 75 to 1000 mg C_{max} and AUC values were linearly related to dose (r^2 = 0.937–0.979). The i.m. dose was 100% bioavailable. The concentrations of trospectomycin in serum were described by bi- or tri-exponential disposition functions indicating initial half-lives of 1.1–2.1 h and terminal half-lives of over 15 h where data were available beyond 24 h (Table 1). Most of the drug was eliminated rapidly (mean residence time 5–12 h). The distribution volume (V_{ss}) was 59–112% of body weight and clearance was 112–152 ml min^{-1}.

Intravenous dosing

The data were best described by a tri-exponential function. However, for 10 subjects the CV of the parameter estimates of the three exponential model were unacceptably high and there were high correlations between parameters indicating overparameterisation. This reflected a lack of data beyond 24 h in these subjects. Therefore, parameters derived from the tri-exponential fit are presented only for subjects in whom concentrations were measured up to 48 h (Table 1). The variability in kinetic parameters between subjects was relatively low (CV < 40%). In most cases < 5% of the AUC was accounted for by the area beyond the last sample. The clearance at the lowest dose was significantly higher than that of the other doses, which cannot be accounted for by the duration of sampling. There was otherwise no effect of dose on clearance.

Intramuscular dosing

A bi-exponential disposition function with first order input adequately described the data in all but seven subjects. These had a relatively slow rise in serum drug concentration and were excluded from the kinetic analysis. There appeared to be a weak, but statistically significant, decrease in the apparent absorption rate constant (k_a) with dose (range of k_a was 2.0–5.2 h^{-1}). Absorption was rapid (t_{max} was 0.7–1.2 h).

There were no significant differences between kinetic parameters at different doses after the i.m. administration (Table 1).

Discussion

Serum concentrations of trospectomycin after all of the doses studied were < 2 μg ml^{-1} by 12 h. Since minimum inhibitory concentrations (Zurenko *et al.*, 1988) for a variety of organisms (e.g. *Neisseria gonorrhoeae, Bacteroides fragilis, Streptococcus* spp.) are 2–4 μg ml^{-1} this suggests that two or three times daily dosing would be appropriate. However, the long terminal half-life indicates that there is a prolonged retention of a small proportion of the dose by some tissues (the terminal phase constituted 15–20% of the total AUC) which may be of clinical relevance for both efficacy and toxicity.

We acknowledge Peter Blood who wrote a SAS program to calculate non compartmental parameters. Steve Wood and Roger Simmonds measured the trospectomycin concentrations.

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(Received 23 January 1990, accepted 25 March 1991)