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Human Safety and Pharmacokinetics of a Single Intramuscular Dose of a Novel Spectinomycin Analog, Trospectomycin (U-63,366F)

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In this study, local and systemic tolerance and pharmacokinetics of trospectomycin sulfate in human beings were evaluated for the first time. Trospectomycin sulfate (U-63,366F; trospectomycin) or sterile saline was administered to 96 healthy male volunteers in doses ranging from 0.25 ml (75 mg) to 3.3 ml (1,000 mg) in a single intramuscular injection in a double-blind, randomized design. Volunteers were screened to establish baseline vital signs and laboratory test values. Pain and tenderness at the injection site, which occurred at doses of 450 mg and above, were the most common side effects; they were mild in severity and transient. Adverse drug experiences reported by subjects included nausea, dizziness, light-headedness, diaphoresis, costal pain, and perioral numbness. The perioral numbness (paresthesia) experienced at doses of 750, 900, and 1,000 mg was probably drug related. No *Clostridium difficile* toxin was detected in fecal samples. Pharmacokinetic calculations based on data obtained by high-performance liquid chromatography showed that after a 1,000-mg intramuscular dose of trospectomycin (3.3 ml), the serum mean half-life was 1.85 h (1.70 to 2.02 h), mean area under the serum concentration-time curve was 140.2 μg · h/ml and was linear with dose, mean peak concentration was 28.3 μg/ml (20.4 to 34.7 μg/ml), mean time to maximum concentration was 71 min (30 to 120 min), and the elimination rate constant was 0.307 h^{-1}. The elimination rate constant and half-life did not vary with dose. Little trospectomycin was detected in 2-day fecal collections. A few randomly occurring abnormal clinical laboratory test values and vital signs were observed. For the trospectomycin-treated group, creatinine phosphokinase increased substantially for 24 h after injection and then decreased through day 5, while serum glutamic oxalacetic transaminase and lactate dehydrogenase increased slightly.

Spectinomycin, an aminocyclitol antibiotic with broad-spectrum antibacterial activity, has been used for many years for the treatment of uncomplicated anogenital gonorrhea. Trospectomycin sulfate (U-63,366F; trospectomycin), an analog of spectinomycin, is crystalline and water soluble (17, 18) and has demonstrated in vitro activity against anaerobic bacteria and against gram-positive and some gram-negative aerobic bacteria including *Chlamydia trachomatis* (20, 21). Trospectomycin is 8 to 10 times more active than spectinomycin and has activity against a spectrum of pathogenic species including species from the genera *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Gardnerella*, *Neisseria*, *Peptococcus*, *Peptostreptococcus*, *Bacteroides*, *Mobiluncus*, *Chlamydia*, *Mycoplasma*, and *Ureaplasma* (5, 12, 19). Trospectomycin is inactive against pseudomonads and has moderate activity against members of the family *Enterobacteriaceae*. The in vitro activity has been confirmed in experimental animal models of human infection (1).

The purpose of the present study was to evaluate, for the first time in humans, the local and systemic tolerances to trospectomycin administered intramuscularly in single doses ranging from 75 to 1,000 mg and to measure drug concentrations in the blood, urine, and feces of healthy subjects following an intramuscular injection.

MATERIALS AND METHODS

Subjects. Ninety-six healthy males from the Upjohn Clinical Research Unit in Jackson, Mich., between 18 and 55 years of age, within 20% of ideal body weight (determined by New York Metropolitan Life Insurance actuary tables), and with normal vital signs and laboratory values were selected for this study. Subjects with a history of allergies or renal or hepatic disease were excluded. In addition, subjects could not have taken antibiotics for the preceding 30 days, any other form of medication for the preceding 2 weeks, or any alcohol 48 h before the start of the study. Subjects had to sign an informed consent form.

Study design. This was a double-blind, single-dose, randomized, placebo-controlled tolerance and pharmacokinetics study in which intramuscular doses of 75, 150, 300, 450, 600, 750, 900, or 1,000 mg (0.25 to 3.3 ml) of trospectomycin or placebo were compared in healthy volunteers by using a pioneer treatment block design. Two weeks before drug administration, subjects were screened for inclusion in the study. Each of 96 subjects who successfully met the screening criteria was randomly assigned to a dose group. Neither the subjects nor the investigator knew the treatment assignments. Two trospectomycin-treated subjects and one saline-treated subject acted as pioneers for each study group by receiving the next higher dose of study drug before the remainder of the subjects were injected at that dose level. No additional subjects were injected until the local and systemic tolerance and safety data from the previously dosed study group and the pioneers for the next group were evaluated. Subjects were assigned to one of eight study groups. A study group was defined as all subjects who received the same volume of injection (eight were treated with trospectomycin, and four were treated with placebo). Trospectomycin (300 mg/ml) or placebo was administered deep in the upper outer quadrant of the right gluteal muscles with a 1.5-in. (3.8-cm) 22-gauge needle. The usual technique of aspirating after needle insertion and before injection was employed to avoid intravascular administration. Subjects

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fasted for 2 h after injection. The tolerance and pharmacokinetic endpoints, as well as the routine laboratory analyses, as described below, began following injection. Blood, urine, and fecal samples were collected for 2 days for pharmacokinetic analyses, and the pain at the injection site was evaluated for 3 days unless it persisted beyond 3 days.

Patient population characteristics. The heights, weights, ages, and body builds of the subjects entering the study were similar for the trospectomycin and sterile saline dose groups. There were no meaningful differences between dose groups in results of the physical examinations given before the study, in vital signs taken before the study, or in electrocardiograms done before injection.

Local tolerance. Both pain and tenderness at the site of injection were evaluated by the same blinded observer. In addition, body temperatures were obtained orally at each pain and tenderness evaluation. If residual pain was still present at the evaluation on day 3, the evaluations continued until the pain subsided. At each evaluation, both the subject and observer assessed the amount of pain and tenderness at the injection site as none, mild, moderate, or severe. The presence of erythema, induration, swelling, ecchymosis, petechiae, necrosis, and atrophy was also noted and assessed as none, mild, moderate, or severe by the observer.

Laboratory assays. Clinical chemistry, hematology, and urinalysis assays were done on samples collected during the screening procedure at zero time, 60 min after injection, and on days 2, 3, and 5 postinjection. Selected enzymes were measured at these times and at 2, 4, 8, and 12 h after the first dose.

Adverse medical events. The medical events of each subject, whether considered to be drug related or not, were recorded on one of two report forms (A or B). Adverse medical event form A was used to report non-life-threatening events and adverse medical event form B was used for life-threatening events. The adverse medical events were evaluated according to preset criteria to determine if they were drug related.

***Clostridium difficile* assay.** Fecal specimens were obtained from subjects before the start of the study and at intervals up to 48 h after injection and were assayed for the presence of *C. difficile* cytotoxin by utilizing the Mayo Clinic procedure (6). This two-stage microbiologic assay was used to test for the presence of the toxin in fecal samples of subjects before and after injection. The first stage involved the inoculation of MRC-5 cell cultures with a stool preparation followed by observations for cytopathic effects. In the second stage, for those cultures found positive, the assay was repeated with the addition of a *C. difficile*-specific antitoxin to the culture medium along with the fecal preparation. If the cytotoxin was neutralized, the cultures did not show cytopathic effects, which indicates the presence of *C. difficile* in the fecal samples.

Microbiologic agar plate assay. Trospectomycin levels in urine and feces were measured by a microbiologic plate assay at the Upjohn Clinical Research Laboratory in Kalamazoo, Mich. Briefly, *Staphylococcus epidermidis* (UC9930), the test organism, was grown in trypticase soy broth and used to inoculate a petri plate containing a semisolid medium. Cylindrical wells punched in the medium were filled with the appropriate biological fluids (i.e., serum, urine, or fecal preparation) which had been collected from the subjects and allowed to incubate for 16 to 18 h. The diameters of the zones of inhibition of growth of *S. epidermidis*, which correlated with the amount of trospectomycin in the sample, were measured and recorded.

The limit of quantification in biological fluids was 0.75 μg/ml with a coefficient of variation (CV) of 10% or better. The assay was shown to be linear over the trospectomycin concentration range of 0.75 to 12.0 μg/ml. The CVs for the standard points ranged from 0.5 to 5.3%. Recovery of replicate controls at 2 μg/ml, for six runs, was 1.92 μg/ml (96%) with a CV of 6.3%, and the within-day CVs ranged from 3.1 to 8.6%.

HPLC assay. Serum samples were also assayed for trospectomycin by a high-pressure liquid chromatography (HPLC) method at the Pharmaceutical Research Laboratory, Upjohn Ltd., Crawley, United Kingdom. The method involves solid-phase extraction of 6′-propylspectinomycin (trospectomycin sulfate) and 6′-butylspectinomycin (as internal standard) from 0.5 ml of biofluid, efficient reversed-phase HPLC with postcolumn oxidation, reaction with *o*-phthaldialdehyde, and fluorescence detection (13).

The limit of quantification in serum was 0.010 μg/ml with a CV of 15% or better. Over the range of 0.025 to 15 μg/ml, the plot of peak height ratios of trospectomycin to internal standard was linear ($r > 0.999$; $n = 20$). Replicate calibration graphs of 7 points in duplicate, in the range of 0.1 to 10 μg/ml, gave an average value for r of 0.996 with a CV on the slope of 3%. Satisfactory precision (CV < 10%) was shown throughout the concentration range both between and within assays. For example, over 13 analytical runs for a low-concentration sample (nominally 0.022 μg/ml), the within- and between-assay CVs were 5 and 3.7%, respectively.

Serum samples. Blood (25 ml) was obtained by venipuncture immediately after injection of the test article, and 10 ml was obtained at the following preset times: 10, 20, 30, 60, and 90 min and 2, 3, 4, 6, 8, 12, 18, 24, 48, and 96 h postinjection. The time of blood withdrawal was recorded on the label. Serum (4.0 ml) was harvested from all blood, divided into two aliquots, frozen, and shipped to the appropriate laboratories for drug level testing by using microbiologic agar plate and HPLC assays described above.

Urine samples. Urine was collected at zero time (before medication was injected), at 2, 4, 8, 12, and 24 h, and at day 2 postinjection. The collection time and volume collected were recorded, including two pooled urine volumes (taken from 0 to 24 and from 24 to 48 h). From each collection period, 10 ml of well-mixed urine from each subject was shipped to the appropriate laboratory to be tested for levels of trospectomycin by the microbiologic agar plate assay.

Fecal samples. Fecal excretions were collected for a total of 48 h. Each fecal excretion was collected and weighed individually. For each subject, all samples were homogenized with an appropriate volume of 0.1 M phosphate buffer, pH 8.0, and the volume was recorded. A 30-ml sample of each homogenate was transferred to a container, frozen, and shipped to the appropriate laboratory to be evaluated for trospectomycin levels by the microbiologic agar plate assay.

Statistical analyses. Results from qualitative response variables (e.g., urine color) were not analyzed statistically but instead only listed or tabulated. For continuous response variables (e.g., vital signs and most of the laboratory assays), paired Student's t tests were performed to identify statistically significant changes across time and within treatment groups. Statistically significant treatment differences associated with continuous response variables were identified by using a univariate, repeated measure analysis of covariance model that incorporated treatment, linear dose, and time effects along with the associated interaction. The baseline response was used as a covariate, while the baseline

TABLE 1. Estimated increase of CPK values from baseline for trospectomycin-treated and placebo-treated subjects

Treatment (*n*)	Mean increase of CPK value (IU/liter) from baseline at day:							
	1, h:					2	3	5
	1	2	4	8	12			
Trospectomycin (63)	7.1	19.7	43.6	59.0	72.1	44.1	34.1	4.1
Placebo (32)	7.5	8.8	10.3	7.5	5.7	−4.2	−3.6	−4.2

minus the follow-up score was treated as the dependent variable.

The concentration-time data obtained by HPLC were fitted with a two-compartment model with first order absorption by using NONLIN84 (16). The apparent serum clearance rate, volume of distribution at steady state, rate constants of absorption, elimination, and distribution, initial volume of distribution, and initial and terminal half-lives were calculated by using NONLIN84. The areas under the concentration-time curve for the HPLC data were calculated by the linear trapezoidal rule from the time of injection to the time of maximum concentration and by the log trapezoidal method from the time of maximum concentration to the last sampling time. The area from the last sampling time to infinity was obtained by using the exponent, beta, of the compartmental model. The total area under the concentration-time curve combined these three values.

RESULTS

Demographic data. The mean weights of the subjects did not change over time for either the treatment or the placebo groups. A large portion of the subjects, 72% of trospectomycin-treated and 75% of placebo-treated subjects, were smokers.

Vital signs, electrocardiograms, and physical exams. There were no trends, clinically meaningful changes, or statistically significant differences seen when the vital signs of trospectomycin-treated subjects were compared with those of placebo-treated subjects. Results of electrocardiograms done 24 h after injection showed no drug-related changes. Physical examinations before and at the end of the study did not reveal any abnormal findings in any of the subjects.

Laboratory analyses. No abnormalities, trends, or changes of clinical importance were observed in the hematology assays or the standard clinical chemistry assays, with the exception of the creatine phosphokinase (CPK) values. There were, however, statistically significant treatment differences or treatment interactions for assays for the following: leukocyte counts, percent monocytes, percent basophils, serum phosphorus, serum glutamic oxalacetic transaminase, lactate dehydrogenase (LDH), and CPK. For all assays except CPK, these differences were not clinically meaningful and had no particular pattern or trend. Most laboratory test values were within the normal range of values for the given assay.

For CPK, time-treatment, treatment-dose, and time-treatment-dose interactions were statistically significant (P = 0.0001, 0.0012, and 0.0038, respectively). The estimated mean increases of CPK values from baseline for the time-treatment interactions are shown in Table 1. At h 2 and beyond, the mean CPK values, averaged over all dose levels, increased from baseline more in the trospectomycin-treated subjects than in the placebo-treated subjects. For the trospectomycin-treated subjects, the mean estimates increased in a linear fashion through day 1, h 12, and then decreased through day 5.

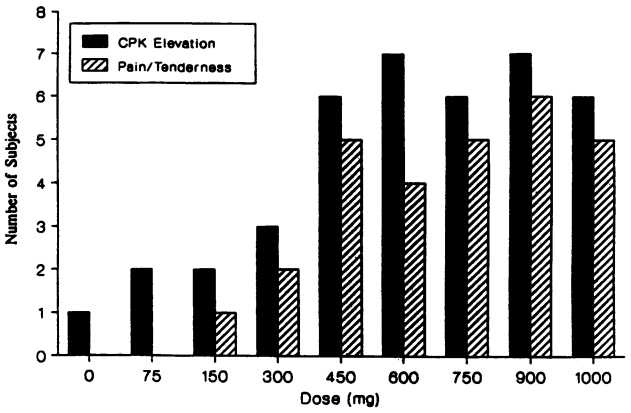

FIG. 1. Number of subjects with elevated CPK and pain and tenderness for each dose group (n = 32 for the placebo-treated [0 mg] group; n = 8 for each trospectomycin-treated group).

Estimated slopes for the treatment-dose interactions were 15.2 IU/liter for the trospectomycin-treated subjects and −4.6 IU/liter for the placebo-treated subjects. This indicated that on the average, CPK values increased approximately 15 IU/liter for each 1-ml (300 mg/ml) increase in dose for the trospectomycin-treated subjects, in contrast to the placebo-treated subjects for whom CPK levels decreased nearly 5 IU/liter for each 1-ml increase in dose.

Urinalysis. No abnormalities, trends, or changes of clinical importance occurred in the urinalyses, which included routine urinalysis, β_2-microglobulin assay, creatinine clearance assay, and urine volumes.

Injection site evaluation. Pain (subjective assessment) and tenderness (objective assessment) were the most frequently

TABLE 2. Frequency of reported side effects at the injection site for each dose group

Group (no. in each group) and side effect	Frequency of side effects at the following dose (ml)[a]:							
	0.25	0.5	1	1.5	2	2.5	3.0	3.3
Trospectomycin-treated (8)								
Sensation of pressure or tightness	1		1	1		1	1	
Feeling of heaviness				1				
Mild tenderness		1	4	4	2	6	4	2
Mild pain			1	1	4	5	5	5
Moderate pain								1
Burning				1				
Bleeding				1	2	1		
Muscle cramp					1			1
Feeling of hardness						1		
Feeling of numbness						1		
No. of subjects with side effects	1	1	4	5	7	8	6	6
Placebo-treated[b] (4)								
Bleeding			1					
Mild tenderness			1					
Mild pain						1		
Slight sting						1		
No. of subjects with side effects	0	0	1	0	0	2	0	0

[a] Trospectomycin at concentration of 300 mg/ml.
[b] Placebo was sterile saline.

TABLE 3. Adverse medical events reported by those who received a placebo or trospectomycin sulfate

Subject no.	Dose (mg)	Vol (ml)	Medical event(s) reported
80	0	3.0	Nausea and light-headedness
2	75	0.25	Mild tenderness and dizziness
7	75	0.25	Mild right costal pain
65	750	2.5	Tenderness at injection site and hip
68	750	2.5	Nausea, dizziness, and diaphoresis; numbness in mouth
73	900	3.0	Mild numbness in teeth
79	900	3.0	Chills, dizziness, and light-headedness
83	900	3.0	Flushing, nausea, vomiting, and light-headedness
90	1,000	3.3	Light-headedness, numbness in gums, and difficulty in focusing eyes
91	1,000	3.3	Numbness in gums
92	1,000	3.3	Numbness in gums
96	1,000	3.3	Numbness in gums, muscle tightness in face

reported side effects that occurred at the injection site. Figure 1 shows the number of subjects who reported pain and tenderness for each dose group. Among those reporting pain, only one subject, who received the highest dose of trospectomycin (1,000 mg [3.3 ml]), reported moderate pain; all others reported mild pain. In all cases, the pain and tenderness were transient; they started immediately after injection and lasted up to 8 h. All the reports of side effects at the site of injection are summarized in Table 2. In general, trospectomycin caused some dose-dependent pain or tenderness at the injection site or both but was well tolerated by most subjects.

CPK and pain correlation. Reports of pain and tenderness were much higher for subjects who received trospectomycin than for those who received a placebo, with the highest incidence in the groups who received from 300 (1.0 ml) to 1,000 (3.3 ml) mg of trospectomycin. No other signs of intolerance at the injection sites were noted during the study. Of 64 subjects injected with trospectomycin, 39 (61%) had CPK values that increased 40 U or more from the baseline; 28 (72%) of these 39 had pain at the injection site. Overall, 28 subjects (44%) had both increased CPK and pain. Among the 34 trospectomycin-treated subjects reporting pain, 28 (82%) had elevated CPK values at follow-up. Of the 30 who did not report pain at the injection site, only 11 (37%) had elevated CPK values. This difference was statistically significant ($P = 0.002$). Of the 32 subjects treated with a placebo, 2 reported pain at the injection site and 1 had an increased CPK value.

Adverse medical events. Eleven of the 64 trospectomycin-treated subjects and 1 placebo-treated subject reported adverse medical events. Perioral numbness (paresthesia) was reported by 6 (25%) of the 24 subjects from the 750-, 900-, and 1,000-mg-dose groups. No other drug-related medical events or trends were observed clinically. Table 3 is a complete list of all adverse medical events reported.

***C. difficile* toxin assay of stool specimens.** Of the 189 stool specimens submitted for *C. difficile* toxin assay, 22 exhibited cytopathic effects within 48 h of inoculation of MRC-5 cell cultures. Three specimens from the pretreatment collections were positive, and 19 from the collections taken day 1 and 2 posttreatment were also positive; however, none of the cytopathic effects were neutralized by *C. difficile*-specific antitoxin. Accordingly, the original cytopathic effects were not attributable to the cytotoxin of *C. difficile*.

Pharmacokinetic parameters. Data derived by HPLC assay (to measure trospectomycin levels in serum) were fitted to a two-compartment model. Table 4 provides a summary of some of the pharmacokinetic parameters for each dose group.

The concentrations of trospectomycin in serum (HPLC method) were plotted over time for each dose group for 96 h after injection (Fig. 2). The curves are approximately parallel, which indicates that the half-life is independent of the dose given. The concentrations of trospectomycin in serum were less than 2 μg/ml by 12 h postinjection at all dose levels.

The area under the concentration curve was linearly related to dose (Fig. 3). The concentration maximum was also linearly related to dose (Fig. 4).

Urinary and fecal levels of trospectomycin. Thirty-five to 50% of the doses were excreted in the two combined 24-h urine collections as shown in Table 5. Very little drug was measured in the fecal samples (Table 5). When the fecal recovery totals were added to the amount detected in the two 24-h urine collections, the total percentage of recovery of trospectomycin changed very little. Thus, the urine is the primary route of excretion.

DISCUSSION

Comparisons of the structural formulas of the commonly used aminocyclitol antibiotics have shown that streptomycin, kanamycin, and gentamicin are actually aminoglycosides and that spectinomycin and trospectomycin are non-aminoglycosidic. Trospectomycin and spectinomycin are fused tricyclic molecules containing a unique aminocyclitol (actinamin) but no amino sugar (3). With present knowledge, we can speculate that the amino sugar portion(s) of a compound and perhaps its position in the molecule regulate the degree of toxicity (ototoxicity and nephrotoxicity). In

TABLE 4. Pharmacokinetic parameters of trospectomycin[a]

Dose (mg) (*n*)	C_{max} (μg/ml)	AUC (μg · h/ml)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	MRT (h)
75 (8)	3.2 ± 0.557	11.0 ± 1.976	1.7 ± 0.143	32.0 ± 8.294	11.37 ± 1.949
150 (8)	5.5 ± 0.708	20.2 ± 2.517	1.7 ± 0.177	25.4 ± 9.661	8.41 ± 2.774
300 (6)	10.2 ± 2.328	41.6 ± 4.068	1.9 ± 0.283	27.1 ± 7.529	8.61 ± 2.075
450 (6)	14.1 ± 3.945	63.3 ± 8.629	1.8 ± 0.184	35.8 ± 3.487	11.22 ± 1.503
600 (8)	19.3 ± 2.572	80.3 ± 12.910	1.9 ± 0.351	34.4 ± 9.768	10.61 ± 2.374
750 (8)	22.8 ± 3.727	102.6 ± 10.464	2.1 ± 0.292	31.0 ± 3.934	9.02 ± 2.198
900 (7)	25.3 ± 5.625	121.0 ± 18.308	2.0 ± 0.292	31.9 ± 10.120	9.51 ± 2.742
1,000 (6)	28.3 ± 5.062	140.2 ± 12.305	1.8 ± 0.142	22.9 ± 5.613	8.81 ± 2.026

[a] All values are given as mean ± standard deviation. C_{max}, Maximum concentration of drug in serum; AUC, area under the concentration-time curve; $t_{1/2\alpha}$, half-life at α phase (indicating distribution into tissues); $t_{1/2\beta}$, half-life at β phase (indicating distribution equilibrium between plasma and tissue); MRT, mean residence time.

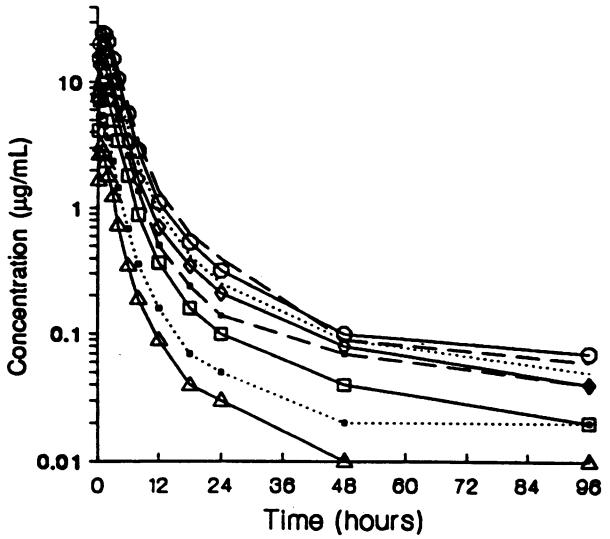

FIG. 2. Levels of trospectomycin in serum following a single intramuscular dose. Doses were 75 (△), 150 (···■···), 300 (□), 450 (--■--), 600 (◇), 750 (·····), 900 (○), and 1,000 (– – –) mg.

multiple-dose intramuscular and intravenous studies with spectinomycin in normal human subjects, no ototoxicity or nephrotoxicity was noted (7, 8). Similar data for trospectomycin will be accumulated. Streptomycin, gentamicin, and other aminoglycoside antibiotics are known to have neuromuscular transmission-blocking properties. Such paresthesia could also be a lidocainelike local anesthetic effect, since local anesthetics (e.g., lidocaine) in serum at levels of or near 5 µg/ml are known to cause paresthesia or perioral paresthesia (2).

In the present study, perioral numbness (paresthesia)

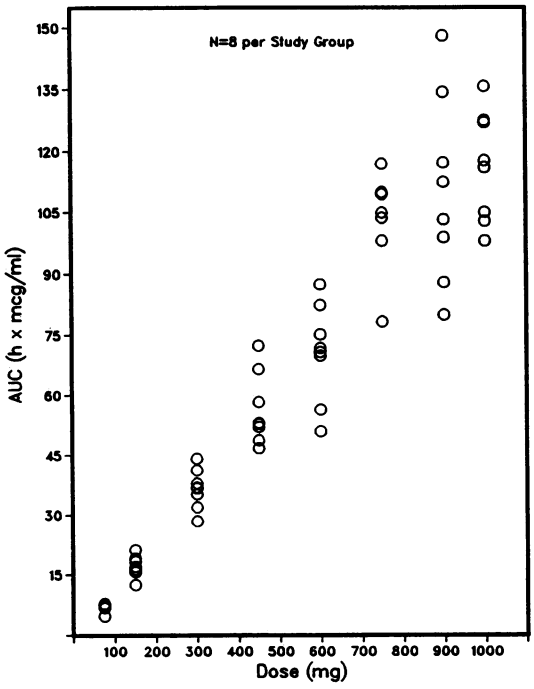

FIG. 3. Area under the serum curve (AUC) for trospectomycin from 0 to 18 h postinjection. Each circle represents one subject.

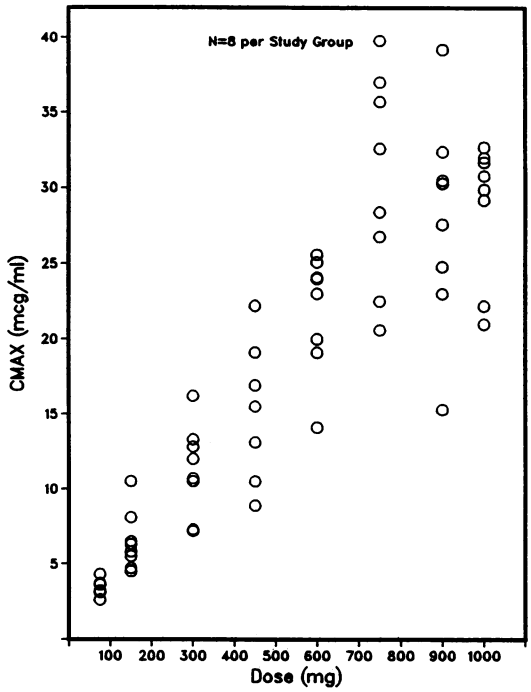

FIG. 4. Maximum concentration of trospectomycin in serum (CMAX). Each circle represents one subject.

occurred with the 750-, 900-, and 1,000-mg doses. It was mild in severity, transient, and probably due to the interference of trospectomycin with calcium entry into the nerve endings.

Animal studies indicated that the aminoglycosides inhibit prejunctional release of acetylcholine while also reducing postsynaptic sensitivity to the transmitter (10, 14). Calcium overcomes the effect of the aminoglycoside at the neuromuscular junction. The intravenous administration of a calcium salt is the preferred treatment of this toxicity (15). Inhibitors of cholinesterase (edrophonium and neostigmine) have also been used with various degrees of success. Acute muscular paralysis and apnea resulting from neuromuscular blockade have been attributed to the various aminoglycosides; neomycin was implicated as the most frequent cause (11). In experimental systems, the order of decreasing potency is neomycin, kanamycin, amikacin, gentamicin, streptomycin, and tobramycin. Trospectomycin blocked neuromuscular transmission and caused hypotension in the isolated nerve-muscle preparation in anesthetized cats (unpublished data, The Upjohn Company, 1988). Trospectomycin given intravenously in high doses (over 100 mg/kg) to dogs caused a reduction in neuromuscular transmission characterized by muscular weakness (unpublished data, The Upjohn Company, 1986).

In humans, neuromuscular blockade has generally occurred after intrapleural or intraperitoneal instillation of large doses of an aminoglycoside; however, the reaction has also followed the intravenous, intramuscular, and even the oral administration of these agents (4). Most episodes have occurred in association with anesthesia or with the administration of other neuromuscular transmission-blocking agents. Patients with myasthenia gravis are particularly susceptible to this effect. However, others who depend on various degrees of hypoxemia to drive respiration (e.g., patients with chronic obstructive pulmonary disease) should be observed carefully for signs of respiratory depression when an aminoglycoside is administered.

TABLE 5. Recovery of trospectomycin[a]

Dose (mg)	Total amt of drug recovered (mg)		% of dose recovered	
	Urine	Feces	Urine	Feces
75	28.1	1.3	37.5	1.8
150	52.6	2.0	35.1	1.3
300	133.3	1.5	44.4	0.5
450	160.7	1.8	35.7	0.4
600	291.2	2.0	48.5	0.3
750	365.5	2.9	48.7	0.4
900	362.8	2.3	40.3	0.3
1,000	477.8	3.1	47.8	0.3

[a] Recovery from urine and feces of healthy volunteers following intramuscular administration of a single dose (microbiologic assay).

In this study, the CPK enzyme levels were elevated 40 IU/liter or more in 61% of the subjects who received trospectomycin. The increases were not considered to be medically important. Measurements of CPK isoenzyme showed that this enzyme was generated in skeletal muscle rather than in cardiac muscle or brain tissue. Muscle trauma is known to increase CPK activity. When CPK assays were less sensitive, it was believed that only irritating drugs caused increases in CPK activity. It is now known that even minimal exercise can increase CPK activity (9). Single injections of several types of drugs, including diuretics, antibiotics, and analgesics, can produce CPK values two to six times larger than normal values, and 20-fold elevations have been reported following multiple injections of these drugs (9).

Utilization of the HPLC assay (sensitivity, <0.020 μg/ml) on specimens collected over a 96-h period demonstrated that the concentrations at the late times had been underestimated when the one-compartment model was used. Use of a first-order-absorption two-compartment sums-of-exponentials model showed an alpha half-life of 1.6 to 2.1 h and a beta half-life of approximately 23 to 36 h. This persistence of the drug is believed to be due to its retention by body organs, which has been demonstrated in animals (A. Bye and L. G. Dring, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 272, 1987).

Previous pharmacokinetic studies of trospectomycin in animals indicated that the drug is not metabolized, that it is excreted mainly in urine (with a clearance rate equivalent to the glomerular filtration rate), that its elimination is biphasic, with up to 70% of the drug eliminated within 12 h, and that the remaining tissue-associated drug is excreted more slowly. When trospectomycin concentrations in serum in humans were measured for a long enough duration after dosing (>24 h), the disappearance of drug followed a biphasic (biexponential) pattern with half-lives of 1.2 to 1.9 and 17 to 36 h. At the higher doses (>750 mg), the concentrations in serum were sustained above 1 μg/ml for 12 h. The absorption into blood after intramuscular dosing was rapid, with a mean absorption time of 0.3 h (Bye and Dring, 27th ICAAC). The low recovery of drug in the urine is due in part to its degradation upon storage and in part to the long retention time in tissues, which is a subject under investigation.

Under the conditions of this study, trospectomycin was well tolerated and caused fewer adverse side effects than are generally seen with other aminocyclitols. Trospectomycin is readily absorbed, reaches therapeutic levels, and is excreted primarily by the urinary route. A similar study using a single intravenous infusion in normal males is planned.

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