Absence of Otoxicity of Teichomycin A2 in Guinea Pigs

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Teichomycin A2 is a new antibiotic that is similar to vancomycin. Because vancomycin is reported to be ototoxic, teichomycin A2 was tested for ototoxicity. No evidence of ototoxicity was found. Furthermore, ethacrynic acid, a diuretic that augments the ototoxicity of many drugs, did not enhance ototoxicity with teichomycin A2.

Teichomycin A2 (teicoplanin) is a new antibiotic first isolated from “Actinoplanes teichomyceticus” by Parenti et al. (12). It is a glycopeptide antibiotic like vancomycin, but it differs chemically (1, 3). Like vancomycin, teichomycin A2 exerts its antibacterial activity by interfering with bacterial cell wall synthesis (13).

The in vitro antibacterial activity of teichomycin A2 compares very favorably to that of vancomycin against a large number of gram-positive bacteria, including penicillin-resistant staphylococci (8). Thus, it appears that teichomycin A2 is a potentially useful antibiotic.

Because teichomycin A2 appears to be a promising antibiotic similar in many respects to vancomycin, which has been reported to be ototoxic (11), the ototoxic potential of teichomycin A2 should be determined. This study was performed to determine whether teichomycin A2 is ototoxic in guinea pigs.

Teichomycin A2 tromethamine salt was dissolved in a 2.5% solution of polyvinylpyrrolidone. Both the polyvinylpyrrolidone and the teichomycin solutions were made fresh daily. A total of 54 guinea pigs was used. Twenty-one animals were used in a repeated-dose study, eighteen were used in a single-dose pharmacokinetic study, and fifteen were used in combination with ethacrynic acid in an interaction study.

The total daily subcutaneous dose of teichomycin A2 of 75 mg/kg (body weight) was divided into three 25-mg/kg doses. An equivalent dose of the vehicle (2.5% polyvinylpyrrolidone) was given to the control animals.

The animals were treated for 28 days. The presence or absence of the Preyer pinna reflex was determined daily, and the animals were weighed every other day for drug dose adjustments. On the last day of drug administration, blood and perilymph samples were taken 4 h after the last 25-mg/kg dose from four animals for drug assay. The remaining 17 animals were maintained in the colony for an additional 14 days; during the next 8 days, these animals were evaluated for cochlear function, and the cochleae were prepared for surface preparation evaluation. The details of the procedure for making the electrophysiological measures and cochlear hair cell counts have been published elsewhere (5–7, 10).

In the single-dose pharmacokinetic study, one 25-mg/kg dose of teichomycin A2 (25 mg/ml in 2.5% polyvinylpyrrolidone) was administered subcutaneously. Blood and perilymph samples were obtained 0.5, 1, 2, 4, 8, 12, and 24 h later. The details of obtaining the blood and perilymph samples have been published previously (6). The samples were assayed by using a slightly modified disk plate microbiological assay (2). The test organism was Bacillus subtilis ATCC 6633 strain B.

In the ethacrynic acid interaction study (9, 14), animals were treated subcutaneously with teichomycin A2 doses of either 75, 150, or 400 mg/kg. Two hours later, each animal was given a single 40-mg/kg dose of ethacrynic acid, or the saline vehicle, intravenously. All guinea pigs were evaluated 4 weeks later for cochlear function, hair cell counts, and the presence or absence of the Preyer pinna reflex. None of the guinea pigs in any of the dosage groups lost its Preyer pinna reflex at any time.

The sound required to generate 1 μV of the alternating-current cochlear potential at each of the 18 test frequencies in the teichomycin A2-treated animals was essentially identical to the data obtained from the vehicle-treated animals.

The sound intensities required to elicit the N1 response threshold at the six test frequencies are shown for the study animals in Fig. 1. This measure is an indication of the capability of the auditory nerve to be activated by sounds. No differences in the N1 thresholds were observed between the teichomycin A2- and vehicle-treated animals (Fig. 1).

The results of the hair cell counts revealed no differences in the loss of cochlear hair cells between the animals treated with teichomycin A2 (2.5%) or the vehicle (2.7%). The average concentration of teichomycin A2 in the blood samples taken from the guinea pigs 4 h after their last dose was 71.8 ± 5.9 (standard deviation) µg/ml. These data indicate that the drug was absorbed into the blood of the treated animals. However, this is the concentration in blood resulting from the repeated subcutaneous administration of teichomycin A2 (25 mg/kg) three times a day for 28 days. So that we would have data as to how these concentrations relate to those obtained after a single 25-mg/kg dose, the single-dose pharmacokinetic experiment was performed. The peak concentration of approximately 30 µg/ml occurred between 4 and 8 h after a single subcutaneous injection. The peak concentration of teichomycin A2 in the blood resulting from the single-dose experiment was about half of that found in the repeated-dose experiment. This indicates that drug accumulation occurred during this experiment.

No teichomycin A2 was found in any of the perilymph samples from the animals treated with teichomycin in the repeated-dose study or the single-dose study. The limit of sensitivity of our assay was 7.2 µg of teichomycin A2 per ml in a 5-µl sample when a 3.7-mm-diameter disk was substituted for the 6-mm disk. It is assumed that the concentration in the perilymph was lower than this concentration.

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Acid Teichomycin (mg/kg) dose and treated animals. This dosage regimen produced no evidence of ototoxicity. As a further check of possible ototoxicity, single doses of up to 400 mg of teichomycin per kg were given to guinea pigs and followed in 2 h by a single 40-mg/kg dose of ethacrynic acid. No evidence of ototoxicity was found. The combined administration of many ototoxic antibiotics, such as viomycin, capreomycin, fortimicin, all of the aminoglycoside antibiotics, and even cisplatin, plus ethacrynic acid has been shown to result in a greatly augmented ototoxicity (4, 5, 9, 14). It is concluded that with the doses used in this study, teichomycin A2 is not ototoxic in guinea pigs.

**LITERATURE CITED**


**TABLE 1.** Maximum alternating-current cochlear potential from guinea pigs treated with the indicated drugs

<table>
<thead>
<tr>
<th>Teichomycin dose (mg/kg)</th>
<th>Ethacrynic acid dose (mg/kg)</th>
<th>Maximum cochlear potential (mean μV ± SD)* at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 kHz</td>
</tr>
<tr>
<td>75</td>
<td>40</td>
<td>1,358 ± 265</td>
</tr>
<tr>
<td>75</td>
<td>None</td>
<td>1,372 ± 309</td>
</tr>
<tr>
<td>150</td>
<td>40</td>
<td>1,492 ± 99</td>
</tr>
<tr>
<td>400</td>
<td>40</td>
<td>1,600 ± 337</td>
</tr>
<tr>
<td>400</td>
<td>None</td>
<td>1,300 ± 394</td>
</tr>
</tbody>
</table>

* n = 3 (six ears) for each treatment group. Most normal guinea pigs that received no treatment were able to generate between 1,300 and 1,500 μV at 1 kHz and between 300 and 500 μV at 10 kHz.

The alternating-current cochlear potential data from the animals treated with teichomycin plus ethacrynic acid are shown in Table 1. None of the animals in any of these treatment groups exhibited any ototoxic effects. Teichomycin A2 (75 mg/kg per day) was administered subcutaneously for 28 days. This dosage regimen produced no evidence of ototoxicity. As a further check of possible ototoxicity, single doses of up to 400 mg of teichomycin per kg were given to guinea pigs and followed in 2 h by a single 40-mg/kg dose of ethacrynic acid. No evidence of ototoxicity was found. The combined administration of many ototoxic antibiotics, such as viomycin, capreomycin, fortimicin, all of the aminoglycoside antibiotics, and even cisplatin, plus ethacrynic acid has been shown to result in a greatly augmented ototoxicity (4, 5, 9, 14). It is concluded that with the doses used in this study, teichomycin A2 is not ototoxic in guinea pigs.

**FIG. 1.** Average sound intensity required to elicit an N1 threshold at each of the test frequencies in the animals treated with teichomycin and those treated with the vehicle. The shaded area represents the range of data from the teichomycin A2-treated animals.

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