Efficacy of Aztreonam in Treatment of Experimental Syphilis in Rabbits

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The efficacy of aztreonam (SQ 26,776) in the therapy of active syphilis infection was evaluated in the rabbit model. Aztreonam was effective in treating active syphilis at a dose of 25 mg/kg given intramuscularly twice daily for 10 days; doses of 2.5 and 0.25 mg/kg were not effective.

Aztreonam (SQ 26,776) is a synthetic monocyclic β-lactam antimicrobial agent which is stable to most β-lactamases (11, 12). In vitro efficacy has been demonstrated against numerous gram-negative bacteria, including Neisseria gonorrhoeae (12). Because of the frequency of coinfection with N. gonorrhoeae and Treponema pallidum in certain populations, it is particularly important to evaluate antimicrobial agents intended for use in gonorrhea therapy for their activity against T. pallidum. The efficacy of the related penicillins and cephalosporins (2, 3, 5, 6, 10) in syphilotherapy suggests that aztreonam might also prove effective for syphilis. This report describes an evaluation of aztreonam as therapy for syphilis in the rabbit model.

Adult male New Zealand white rabbits with no clinical or serological evidence of infection with Treponema paraluisicuniculi were used for this study. T. pallidum (Nichols strain), maintained in rabbits as previously described (8), was extracted from infected testes in sterile 0.14 M saline with 10% heated (56°C for 30 min) normal rabbit serum and adjusted to 5 × 10⁷ T. pallidum per ml (9). Twenty rabbits, divided randomly into five groups, were injected intradermally on the clipped back at each of 10 sites with 0.1 ml of treponemal suspension (5 × 10⁶ T. pallidum per skin site). When syphilitic lesions reached a diameter of 8 to 10 mm (6 days postinfection), material aspirated from one lesion on each animal was examined by dark-field microscopy for motile T. pallidum.

After the first dark-field examination, aztreonam (E. R. Squibb & Sons, Princeton, N.J.) was administered intramuscularly to three groups of animals at doses of 0.25, 2.5, or 25 mg/kg of body weight, twice daily for 10 days. Benzathine penicillin G (Wyeth Laboratories, Philadelphia, Pa.) was administered to one group of animals (200,000 U per week for two injections at a 1-week interval). A fifth group of rabbits remained untreated.

Lesions were examined and measured daily for 10 days after initiation of therapy. Rabbits were observed three times weekly thereafter for a period of 3 months for evidence of appearance of disseminated lesions. Daily, during the 10-day period of antimicrobial therapy, exudate was obtained from one lesion on each rabbit for examination by dark-field microscopy. Lesions were determined to be dark-field positive (DF⁺) if one motile treponeme was observed and dark-field negative (DF⁻) if no motile treponemes were seen during the examination of 100 microscope fields in each of two separate aspirates. Treated animals which had DF⁺ lesions after completion of the treatment regimen were considered to be treatment failures and were not evaluated further. Popliteal lymph nodes were removed (9) from each animal which showed no clinical evidence of persistent or recurrent infection and minced into sterile saline containing 50% normal rabbit serum; the extracted material was injected intrathecally into serologically nonreactive recipient rabbits. The recipient rabbits were examined regularly for 3 months for clinical (development of DF⁺ orchitis) or serological (seroconversion in Venereal Disease Research Laboratory and fluorescent treponemal antibody-ABS tests) evidence of transferred syphilitic infection. Serological tests were performed as described in the Manual of Tests for Syphilis (13) with known negative and positive sera as controls. The fluorescent treponemal antibody absorption technique was modified for use with rabbit serum (7).

As shown in Table 1, untreated control rabbits developed large DF⁺ ulcerative lesions reaching a mean diameter of 14.3 ± 2.5 mm on day 10. On the other hand, T. pallidum could not be demonstrated in any of the four benzathine penicillin-treated rabbits after day 1 of therapy; the lesions did not ulcerate and had a mean diameter of 1.7 ± 3.5 mm at day 10.

The animals which were treated with 0.25 mg of aztreonam per kg twice daily for 10 days showed a course similar to the untreated control rabbits; the DF⁺ lesions ulcerated and reached a mean diameter of 10.5 ± 3.9 mm on day 10. Aztreonam given at a dose of 2.5 mg/kg twice daily for 10 days resulted in the clearance of demonstrable motile organisms in two of four animals by day 7 of therapy. The lesions had a mean diameter of 8.4 ± 4.8 mm on day 10. No motile treponemes were demonstrable in rabbits which were treated with the highest dose of aztreonam (25 mg/kg, twice daily for 10 days) after day 3 of therapy. The nonulcerative lesions had a mean diameter of 0.6 ± 1.2 mm on day 10.

All untreated animals, four of four animals which received the lowest dose of aztreonam, and two of four animals which received the intermediate aztreonam dosage had demonstrable motile treponemes at the end of therapy and were, thus, considered to be inadequately treated. All other treated animals were evaluated for the presence of persistent T. pallidum by popliteal lymph node transfer to serologically nonreactive recipient rabbits. No clinical or serological evidence of infection was seen in recipients of lymph node material from rabbits which were treated with benzathine penicillin or 25 mg of aztreonam per kg twice daily for 10 days. On the other hand, lymph nodes from two rabbits which had been treated with 2.5 mg of aztreonam per kg twice daily for 10 days were determined to be infectious as evidenced by the development of a DF⁺ orchitis and seroconversion in each recipient animal. Thus, although these

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TABLE 1. Summary of therapeutic responses of syphilitic rabbits to aztreonam or benzathine penicillin G

<table>
<thead>
<tr>
<th>Group (dose)</th>
<th>Lesion diam (mm) after 10 days of therapy</th>
<th>No. of lesions with DF* after 10 days of therapy</th>
<th>Mean time to DF** in lesions which became positive</th>
<th>No. of lymph node recipient rabbits developing DF*** of infection</th>
<th>Status of infection in donor rabbit posttherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control</td>
<td></td>
<td>4/4</td>
<td>NA</td>
<td>1/1</td>
<td>Noninfectious</td>
</tr>
<tr>
<td>Benzathine penicillin G</td>
<td></td>
<td>1.7 ± 3.5</td>
<td>0/4</td>
<td>0/4</td>
<td>Noninfective (2)</td>
</tr>
<tr>
<td>(200,000 U per wk for 2 wk)</td>
<td></td>
<td></td>
<td>1.0 (1)*</td>
<td>1/1</td>
<td>Active</td>
</tr>
<tr>
<td>Aztreonam (0.25 mg/kg, twice daily for 10 days)</td>
<td>10.5 ± 3.9</td>
<td>4/4</td>
<td>NA</td>
<td>NA</td>
<td>Active</td>
</tr>
<tr>
<td>Aztreonam (2.5 mg/kg, twice daily for 10 days)</td>
<td>8.4 ± 4.8</td>
<td>2/4</td>
<td>4.5 (2-7)</td>
<td>2/2</td>
<td>Active</td>
</tr>
<tr>
<td>Aztreonam (25 mg/kg, twice daily for 10 days)</td>
<td>0.6 ± 1.2</td>
<td>0/4</td>
<td>2.3 (2-3)</td>
<td>0/3*</td>
<td>Noninfectious</td>
</tr>
</tbody>
</table>

* Lymph node material from animals with DF* lesions was inoculated into susceptible recipient animals to detect persistent latent infection posttherapy. One untreated animal was included as a positive control for lymph node transfer. VDRL, Venerable Disease Laboratory; FTA-ABS, fluorescent treponemal antibody absorption.

** Active, DF* lesions; noninfectious, no seroconversion or clinical manifestations in recipients of lymph node material; latent, no clinical evidence of infection, but lymph node material is infectious.

† Mean ± standard deviation in millimeters.

‡ Number of animals with DF* lesions at completion of therapy/total number of animals.

§ NA, Not applicable.

∥ Number of recipient rabbits with positive result/total number of recipient rabbits.

* Mean (range) in days after initiation of therapy.

a One donor animal died from unrelated causes before lymph node transfer.

animals showed clinical evidence of adequate therapy (lesions which became DF* during the observation period), their lymph nodes contained virulent T. pallidum.

Because of the exquisite sensitivity of T. pallidum to the antimicrobial activity of penicillin G and the lack of evidence for developing antibiotic resistance, it is unlikely that recommended schedules for syphilotherapy will change significantly in the near future. However, as penicillinase-producing strains of N. gonorrhoeae have become more common, the search for alternative gonorrhea therapy has included the expanded spectrum cephalosporins and other β-lactams such as aztreonam. The efficacy of those alternative drugs in therapy for coexisting syphilis infection is of obvious concern.

Because T. pallidum multiplies very slowly, with a generation time of 33 h (1), antimicrobial agents, such as aztreonam (4), which act on dividing cells are effective only if they are present in the host in sufficient concentrations for long periods of time. Aztreonam has been reported to have a mean serum half-life in humans of 1.66 h after a single intravenous dose (11). Only relatively high doses of aztreonam given over a 10-day period were shown by this study to be effective against active syphilitic infection in the rabbit model. Because aztreonam therapy for gonorrhea is likely to be a single-dose regimen, the efficacy of such treatment for coexisting syphilitic infection is dubious. Further, this report illustrates the possibility that administration of subcutaneous dosages of aztreonam or other compounds may result in the resolution of clinical manifestations of syphilis, thus masking the infection, although not effecting a true bacteriological cure.

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LITERATURE CITED


