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Streptomycin
A Review of the Literature

E. H. COLES*, D.V.M., M.S.

STREPTOMYCIN is an antibacterial agent of relatively low toxicity which was isolated by Selman A. Waksman in 1944 from certain strains of the soil actinomycete, Streptomyces griseus.

One of the most outstanding properties of this antibacterial agent is its ability to inhibit the growth of the Gram-negative and acid-fast organisms. It has also been found to inhibit the growth of certain Gram-positive organisms but not to such an extent as to replace penicillin for the treatment of conditions caused by this group of bacteria.

Although there has been a great deal of research in connection with the organisms causing disease in humans, there have been few published reports as to the effect of streptomycin for the treatment of animals. However, many of the reports do contain material which will be of interest to the veterinarian. A large number of organisms which have been studied in vitro are pathogenic to the domestic animals as well as to man.

In vitro Antibacterial Activity: The complete range of the activity of streptomycin has not yet been determined. Many organisms which are found to be pathogenic to domestic animals have been tested in vitro and, although the results are not always duplicated when tested in vivo, such results do indicate a trend towards streptomycin susceptibility. Results of the several in vitro determinations are demonstrated in Table 1.

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It is obvious from Table 1 that there is a great range of streptomycin susceptibility exhibited by the various organisms. In addition to the species variability that exists, a great deal of strain variability has been noted (5, 7). Waksman (3) makes the statement, “The sensitivity of a given culture of an organism to streptomycin is characteristic not only of the organism but of the strain as well.”

Not only is streptomycin strongly bacteriostatic against Gram-negative and Gram-positive bacteria, but it also exhibits a marked bactericidal effect as is pointed out in Table 2, (5).

It will be noted in Table 2, that in the absence of any streptomycin, growth was quite rapid in all 3 cultures. When the organisms were incubated in the presence of 1 microgram of the antibiotic per ml., the numbers were reduced. The addition of 5 micrograms (units) per ml. brought about nearly complete destruction of the cells of the cultures W 1 and W 2 while the reduction of Strain R. (the resistant strain) was appreciably less.

Santivanez (8) has reported that a concentration of 12.5 micrograms per ml. sterilized a broth culture of Pasteurella avicida in 4 hours. A concentration of 6.25 micrograms halted the growth in 12 hours. A culture of Brucella abortus was found to be completely inhibited by 25 micrograms per ml. at the end of 12 hours. Salmonella pullorum was completely inhibited by a concentration of 12.5 micrograms at the end of 24 hours.
TABLE 1
RANGES IN SUSCEPTIBILITY OF BACTERIA TO STREPTOMYCIN

<table>
<thead>
<tr>
<th>Organism</th>
<th>Range—Micrograms Per ml.</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aerobacter aerogenes</em></td>
<td>0.5 - 2.5</td>
<td>1, 2</td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>0.375</td>
<td>3</td>
</tr>
<tr>
<td><em>Brucella melitensis</em></td>
<td>0.5 - 3.75</td>
<td>3</td>
</tr>
<tr>
<td><em>Brucella abortus</em></td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td><em>Brucella suis</em></td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td><em>Clostridium septicum</em></td>
<td>&gt;105</td>
<td>2</td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>&gt;104</td>
<td>2</td>
</tr>
<tr>
<td><em>Erysipelothrix rhusiopathiae</em></td>
<td>2.5 - 10.0</td>
<td>4, 7</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0.3 - 3.75</td>
<td>5</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>0.625- 8.0</td>
<td>6</td>
</tr>
<tr>
<td><em>Malleomyces malleus</em></td>
<td>1.0 &gt;10</td>
<td>3, 7</td>
</tr>
<tr>
<td><em>Mycobacterium avium</em></td>
<td>10.0</td>
<td>4</td>
</tr>
<tr>
<td><em>Pasteurella avipertosa</em></td>
<td>0.5 - 15.0</td>
<td>3, 7, 8</td>
</tr>
<tr>
<td><em>Pasteurella tularensis</em></td>
<td>0.15 - 0.3</td>
<td>3</td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
<td>0.4 - 3.0</td>
<td>5</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2.5 - 25.0</td>
<td>4, 1</td>
</tr>
<tr>
<td><em>Salmonella enterica</em></td>
<td>4.0 - 10.0</td>
<td>1, 2</td>
</tr>
<tr>
<td><em>Salmonella enteritis</em></td>
<td>0.5 - 10.0</td>
<td>2, 7</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0.5 &gt;16</td>
<td>2</td>
</tr>
<tr>
<td><em>Actinomyces bovis</em></td>
<td>3.75</td>
<td>3</td>
</tr>
</tbody>
</table>

Bacteria may acquire a resistance to streptomycin quite rapidly; Buggs et al (9) were among the first to point out this fact. They reported a case in which *Proteus vulgaris*, when first isolated, was found to be sensitive to 2 micrograms per ml and when re-isolated after the patient had been treated with streptomycin was found to require 8 micrograms to inhibit growth. The same was found to be true with a culture of *Pseudomonas aeruginosa*. When tested before treatment it was sensitive to 32 micrograms and after treatment the organism was resistant to 256 micrograms per ml. Such increases have also been reported with the acid-fast *Mycobacterium tuberculosis* (10). Resistance of some strains has been reported to increase 500 to 1,000 fold. Increases in resistance to the antibiotic undoubtedly will play a major role in the use of streptomycin.

Toxicity and Efficacy of Streptomycin in Animals: Studies on the absorption and excretion of streptomycin indicate that when administered parenterally, it behaves much like penicillin in that both antibiotics are absorbed and excreted quite rapidly. Therapeutic blood levels are easily obtained by intravenous, subcutaneous or intramuscular injections but oral administration has been found to produce only a very low blood level (2).

The toxicity of streptomycin has been found to be quite low. This is especially true of the more purified preparations. When toxic results have been noted, they reveal themselves as histamine-like reactions, the visible reactions in mice being increased activity, marked dyspnea and occasionally respiratory failure. This type of toxicity is undoubtedly due to the presence of impurities, as such manifestations are absent when pure preparations are used (2).

Another toxic effect, which is especially pronounced in monkeys, is observed following the prolonged administration of large doses. This occurs as a fatty infiltration of the liver and sometimes the kidney. However, this type of pathology has been shown to be reversible and not the first step of a progressive degeneration. This type of toxicity is not ordinarily noted in rats or mice (11).

Some of the first animal experiments were carried out with a crude preparation of the drug (12). In order to protect...
18-20 gram mice infected with *Salmonella schottmulleri*, 6.4 mg. of crude material was required (the raw material assayed at approximately 30 micrograms per mg.).

Streptomycin was found to be quite active in combatting experimental tularemia in mice (6). In one experiment, in which 30 control mice died of tularemia within 4 days, 30 other mice which received 1,000 micrograms daily for 10 days all survived the infection.

In experimental infections with *Klebsiella pneumoniae*, streptomycin also exhibited a very marked protective effect (13). When doses of 185-500 micrograms were administered daily over a period of 2 or 3 days, 42 of 49 mice survived intraperitoneal inoculation of 1,000 to 10,000 lethal doses of the pathogen. All of the 49 untreated control mice died when the organisms were administered intra-abdominally.

Development of the human strain of *Mycobacterium tuberculosis* in guinea pigs can be controlled by streptomycin. On the basis of an arbitrarily established index of infection, 100 represented the maximum possible amount of tuberculosis. The untreated control animals which were sacrificed at 61 days exhibited an index of 67 as contrasted to an index of 5.8 for those which had received streptomycin. In a second experiment, the values were 81.9 for the untreated and 2.8 for the treated animals. The daily administration of streptomycin varied from 1,387 to 6,000 micrograms (14).

Streptomycin has also been found to exert a repressive effect in experimental infections with *Borrelia novyi* and *Leptospira icterohaemorrhagiae* (15).

![Streptomycin in blood-agar plate exhibiting complete inhibition of Staphylococcus aureus.](image)

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treated with 5,000 micrograms of streptomycin daily, administered subcutaneously in 5 equal doses at 4 hour intervals. At the end of 27 days all of the animals were autopsied. In all of the untreated animals, there was an agglutination titer of 1:100 or higher and a positive culture was made from the inguinal lymph nodes, liver and spleen of all untreated animals. In the treated animals, there were only 4 that showed positive cultures from all 3 sources. The agglutination titer of the treated animals was appreciably less; there were 2 animals with a titer of 1:100 or greater, 4 with a titer of 1:50 and 1 animal with a titer of 1:25.

Benson (17) has reported that streptomycin is an effective antibiotic against Salmonella pullorum in chicks. The organisms were administered intraperitoneally and also given in the water. Streptomycin was administered beginning, in one experiment, 16 hours after inoculation. Doses of 2,500 micrograms were administered at varying intervals up to 72 hours. Of the 26 treated chicks, only 3 died of the disease. Twenty-six other chicks were inoculated with the organisms but not with streptomycin; of these, 23 died.

Summary and Conclusions: It is evident from the present data that very little work with streptomycin in treating animal diseases has accumulated. It is impossible, therefore, to make any conclusions at the present time as to role streptomycin will play in veterinary medicine.

It is apparent, from the existing information, that streptomycin may have application in the treatment of animal diseases caused by some of the Gram-negative organisms.

References


Ground pork or beef which is to be frozen for preservation should not be salted, as salt stimulates oxidation resulting in rancidity; sage, pepper, mace and ginger seem to have an opposite effect.

Winter, 1947