Pharmacology Review:  
Streptomycin, Gentamicin and the Aminoglycoside Antibiotics  

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Streptomycin, discovered by Waksman in 1944, was the second major antibiotic introduced into medicine and the first to result from the great surge in antibacterial research which followed the discovery of penicillin. Discovery of streptomycin was followed by neomycin (1949), kanamycin (1957), gentamicin (1963), tobramycin (1967), and amikacin (1972). Spectinomycin is a closely related antibiotic which is usually grouped with these agents. As a group, these agents are known as the aminoglycoside antibiotics and, more so than any other group of antibiotics, they share a large number of therapeutic, pharmacologic and antimicrobial characteristics in common.

The characteristic which completely dominates the pharmacology of this family of antibiotics is their high water solubility and low lipid solubility. Even casual inspection of the structure of streptomycin (Figure 1) shows it to contain many OH (hydroxyl) and NH groups. These groups interact well with water, and the net result is that streptomycin and the other members of this family cross the lipid membrane of cells with difficulty. They are therefore absorption poorly after oral administration and distribute poorly in the body even if given parenterally. They cross the blood-brain barrier with extreme difficulty, enter the eye poorly, and even have trouble getting into red cells. Because they don’t enter liver cells, they are not metabolized to any significant extent, and are not excreted in the urine. They are therefore excreted largely unchanged by the kidneys, and since they are concentrated by the renal concentrating mechanism, they are found in high concentrations in urine. Because of the many characteristics that this group of drugs has in common, we will present streptomycin, the best characterized drug, as a prototype and then compare the others with streptomycin.

Like all members of this group, streptomycin is essentially not absorbed from the gastrointestinal tract (GIT) and acts only in the GIT after oral administration. For systemic action this drug must be given parenterally, usually by intramuscular (IM) injection. Although well absorbed from an IM injection site, it distributes poorly in the body. If a good central nervous system (CNS) level of streptomycin or any other drug of this group is required, it should be given intrathecally. In general, penetration of these drugs into the CNS is slow, except possibly in cases of meningitis, where the rate of entry is somewhat increased.

As mentioned earlier, the aminoglycosides are excreted largely unchanged through the kidneys, usually by glomerular filtration. Although complete data on the pharmacokinetics of this group of drugs in the horse are not available, their plasma half-lives (in the absence of renal damage) may be expected to be in the order of one and one-half to three hours, and dosage schedules in the order of a half-dose every half-life or a full dose every two to three half-lives are required in order to maintain effective blood levels. Because they are cleared through the kidney, they can attain quite high concentrations in urine. These levels can be 50 to 100 times plasma levels, and drugs of this group may therefore be very effective against urinary tract infections. In addition, streptomycin and other members of this group can be up to 50 times more bactericidal under alkaline conditions, such as is found in many horse urines, so under the right circumstances their antibacterial activity in the urinary tract can be very great indeed.

Streptomycin and the other members of this group are generally considered to be bactericidal drugs, although at low drug concentrations or in the presence of relatively resistant organisms they may be only bacteriostatic. As far as is known, all the members of this group produce their bactericidal effect by binding specifically, and apparently reversibly, to a protein in the bacterial 30S ribosomal subunit. In susceptible bacteria this binding causes disruption of the ribosomal subunit and “misreading” of the information on the messenger RNA. This misreading leads to the synthesis by the bacterium of what are called “silent” or “nonsense” proteins, i.e. “enzymes” without catalytic activity, or “structural proteins” which do not
fit anywhere in the bacterium. This streptomycin-induced inability of the bacterium to synthesize the functional proteins it requires leads to death of the bacterium and accounts for the bactericidal action of streptomycin and the other aminoglycosides.

Because the antibacterial action of streptomycin depends only on its reversible binding by a single protein, any change in this protein can result in loss of streptomycin binding and, thus, in loss of antibacterial activity. Resistance to streptomycin can therefore occur rapidly, and when it does occur, it is usually complete. Apparently what happens is that a single mutation is sufficient to alter the streptomycin binding sites, and once this change occurs, the bacterium is completely resistant to streptomycin. This leads to a therapeutic rule: if a horse has not responded to streptomycin after three days, another antibiotic must be selected, because the organism has likely become resistant to streptomycin. A way around this problem, recommended by some authorities, is never to give streptomycin alone, because combining it with another drug greatly delays the appearance of resistant forms.

Bacterial resistance to aminoglycosides other than streptomycin appears to occur by mechanisms other than ribosomal alteration and does not develop as readily as resistance to streptomycin.\footnote{11} One mechanism apparently involves the reduced uptake of drug by the bacterium. This appears to be the principal mechanism of resistance to amikacin, and resistance to amikacin is usually accompanied by cross-resistance to the other aminoglycoside antibiotics. Another, and clinically more important mechanism of resistance, is due to the elaboration of enzymes which inactivate the antibiotic. Inactivation by this mechanism usually involves the addition of phosphate or adenyl groups to hydroxyl groups on these antibiotics, which interferes with binding of these drugs to their ribosomal receptors. The genes which control production of these phosphorylating or adenylating enzymes are usually carried on extrachromosomal fragments of DNA called "plasmids," which can be transferred by conjugation to other bacteria. These R factors frequently confer simultaneous drug resistance ("infectious drug resistance") to more than one antibiotic. Because of the existence of this R-factor-induced resistance, indiscriminate use of any one aminoglycoside antibiotic seems to be capable of fostering resistance to other members of the group.\footnote{2, 1, 10}

The adverse reactions to the aminoglycoside group of drugs also follow a familial pattern and may be summed up in three phrases: eighth nerve damage, nephrotoxicity, and neuromuscular blockade.

The eighth nerve damage seen after these drugs may be to either its auditory or vestibular branches. Damage to the auditory or cochlear branch, with eventual loss of hearing, is principally associated with use of dihydrostreptomycin, neomycin, or kanamycin.\footnote{2, 1} Damage to the vestibular apparatus with loss of balance and coordination is primarily associated with streptomycin and gentamicin. The reversibility of damage to the auditory branch of the eighth nerve is not clear, and progression of eighth nerve damage after withdrawal of some of these drugs has been seen, except possibly in the case of kanamycin.

This eighth nerve damage appears to be due to the ability of aminoglycosides to penetrate into the inner ear during periods of high plasma concentrations of drug which do not decline during the periods when the plasma concentrations of the drug are low.\footnote{2} These observations have led to the thought that sufficiently low "tough" levels (less than 2 µg/ml of gentamicin) may be important in reducing the incidence of ototoxicity. Of further interest is the fact that experiments with tobramycin have shown small but measurable amounts of cochlear dysfunction after even a single dose of this drug, suggesting that measurable eighth nerve damage begins immediately after administration, which is much sooner than had hitherto been thought. For equine practitioners it is also worth remembering that furosemide\footnote{9} potentiates the ototoxicity of this group of drugs.\footnote{2, 4}

Nephrotoxicity caused by aminoglycoside antibiotics appears as an acute necrosis of the proximal tubular cells of the kidney.\footnote{9} It seems that drugs of this group concentrate in this portion of the kidney and persist there for relatively long periods, with tissue half-lives of up to 100 hours. Among the aminoglycosides, streptomycin is the least nephrotoxic, with gentamicin considered to produce mild abnormalities of renal function in about 8% of recipients. In sharp contrast with eighth nerve damage which tends to be stable or even progressive, renal damage is usually reversible if the drug is discontinued at the first sign of renal dysfunction.\footnote{2, 1, 10}

All the aminoglycoside antibiotics have the ability to produce neuromuscular blockade, but this is usually significant only under special circumstances, such as in postsurgical animals where neuromuscular-blocking drugs have been used. Another circumstance where this effect may be of importance is after application of these drugs to the peritoneal cavity, which sometimes results in apnea. It is thought, in this case, that unusually high concentrations of the drug gain direct access
to neuromuscular junctions in the diaphragm to produce the respiratory arrest. The ability of aminoglycosides to produce neuromuscular blockade is greater for neomycin than for streptomycin, with gentamicin being by far the least likely to produce blockade. Blockade induced by any of the aminoglycosides can be partially or completely reversed by the administration of Ca salts intravenously (IV), while the efficacy of cholinomimetic agents such as neostigmine and edrophonium is highly variable.

Therapeutically, the aminoglycosides are highly effective against anaerobic gram-negative rods which are resistant to less toxic drugs. They are also valuable in association with drugs such as penicillin in the initial therapy of suspected bacteremia. It is, however, important to bear in mind that some pathogens are not covered by frequently used drug combinations, and that many organisms have become resistant to streptomycin. Inspection of the data of Table 1, from Knight et al., shows that a substantial proportion of common equine pathogens are resistant to streptomycin and neomycin, but most are still susceptible to gentamicin. The conditions under which individual drugs of this group are used are therefore quite different, and it is appropriate to discuss their therapeutic uses separately.

At the present time streptomycin is essentially never used alone, and the great bulk of the streptomycin used is in association with penicillin-streptomycin combinations. In combination, penicillin and streptomycin are thought to potentiate each other’s action, probably due to penicillin aiding entry of streptomycin into the bacteria. Together, penicillin and streptomycin give relatively broad antibacterial cover and are usually the first therapy instituted in bacteremia while the results of culture are waited for more definitive identification. About the only problem with penicillin-streptomycin combinations is the fact that streptomycin tends to be cleared more rapidly than penicillin, thus giving rise to intervals in therapy during which penicillin is the only drug present.

Data from Rollins et al. have shown the plasma levels of streptomycin found after administration of penicillin-streptomycin preparations. After 2.5 mg/kg, streptomycin administered as either procaine-penicillin-streptomycin or as a procaine-penicillin-streptomycin-dexamethasone-chloropheniramine combination, serum levels of streptomycin peaked at about 10 μg/ml and fell to about 1 μg/ml over the next 12 hours. If the dose of streptomycin was 3.3 mg/lb as part of a procaine-penicillin, benzathine-penicillin combination, serum levels of streptomycin peaked at about 40 μg/ml and declined at about the same rate as previously. Dihydrostreptomycin therefore has an apparent half-life in equine plasma of about three hours, and for streptomycin alone, Knight recommends doses of 20 mg/kg intramuscularly, three times a day, to maintain plasma levels of this drug. However, because most equine pathogens require substantial levels of streptomycin to inhibit their growth, the clinical usefulness of streptomycin in equine medicine is now quite limited.

Since its introduction into equine medicine, gentamicin has become the most widely used of the aminoglycoside antibiotics and has to a large extent replaced streptomycin. When first introduced into veterinary medicine in the early 1970s, gentamicin was widely active against a large number of animal patho-

| TABLE 1 |

| Percent of common equine pathogens resistant to aminoglycoside antibiotics. |
|-------------------------|-----------------|----------------|---------------------|
| Streptococcus zooepidemicus | 29% | 17% | 0% | 37% |
| Non-hemolytic Streptococcus | 50% | 62% | 20% | 70% |
| Staphylococcus aureus | 53% | 4% | 0% | 5% |
| Salmonella | 75% | 67% | 0% | 67% |
| Proteus mirabilis | 56% | 33% | 0% | 29% |
| Pseudomonas aeruginosa | 83% | 88% | 8% | 47% |
| Pasteurella spp. | 17% | 8% | 0% | 15% |
| Klebsiella pneumoniae | 31% | 6% | 0% | 13% |
| Escherichia coli | 62% | 25% | 0% | 96% |
| Enterobacteraceae | 11% | 10% | 0% | 10% |
| Bordetella bronchiseptica | 100% | 5% | 0% | 5% |
| Corynebacterium equi | 0% | 10% | 0% | 0% |
| Actinobacillus suis and equuli | 39% | 9% | 0% | 16% |
Gentamicin has a broad antibacterial spectrum against gram-negative bacteria, and is very effective against Escherichia coli, Proteus, Klebsiella, Enterobacteriaceae, and Pseudomonas aeruginosa. Salmonella and Shigella are also often gentamicin-sensitive. Estimated minimum inhibitory concentrations of gentamicin for a number of common equine pathogens as reported by Knight et al. are presented in Table 2. Gentamicin is also active against most strains of Staphylococcus aureus, against which it is generally more potent and less ototoxic than kanamycin. Gentamicin, in combination with carbenicillin, is the therapy of choice in treating deep-seated infections with P. aeruginosa. This combination is used because it is both synergistic against the organism and delays the appearance of resistant strains. However, if gentamicin is mixed in the same IV solution as carbenicillin, the combination should be injected at once, because gentamicin slowly loses its antibacterial activity when exposed to carbenicillin.

The use of gentamicin in the treatment of metritis in mares and genital tract infections in stallions has

**TABLE 2**

<table>
<thead>
<tr>
<th>Minimum inhibitory concentration (µg/ml) of gentamicin for equine pathogens</th>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Streptococcus (GPA)</td>
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<tr>
<td>Streptococcus faecalis</td>
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<tr>
<td>Corynebacterium equi</td>
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<tr>
<td>Escherichia coli</td>
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<tr>
<td>Klebsiella spp.</td>
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<tr>
<td>Actinobacillus equuli</td>
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<tr>
<td>Pasteurella hemolytica</td>
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<tr>
<td>Salmonella spp.</td>
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<tr>
<td>Bordetella bronchiseptica</td>
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been reported. In a rather sketchy study, Morrow and co-workers reported on a study in which 60 mares, barren for an average of 3.2 years, were treated with 1 to 2.5 g (2 to 5 mg/kg) of gentamicin daily in about 300 ml of physiological saline as an intrauterine infusion for from one to 10 days. Prior to treatment, about half of these mares were positive for pseudomonas, with streptococci, staphylococci and coliforms making up the balance. After gentamicin treatment, 86% of these mares reportedly had bacteriologically negative uterine cultures, and 74% produced live foals, a substantial percentage of mares to get in foal by any standard. Broadly similar results have also been reported in a study of Houdeshell.

Hamm has reported on the use of gentamicin in the therapy of genital tract infections in three stallions. One of these stallions had bacteriologically confirmed Pseudomonas aeruginosa infection in the genital tract, with decreased sperm count, reduced percentage motility, "liveability," and volume, with an increased number of white blood cells. Another stallion had Klebsiella and Pseudomonas spp. in his semen in association with impaired semen quality. In all of these stallions, treatment at 4.4 mg/kg twice a day, either IM or IV (in the event of muscle soreness) for between 10 and 20 days, eliminated Pseudomonas spp. from the tract of one, and returned each horse to breeding soundness.

Hamm and Jones have reported preliminary results on use of gentamicin in the treatment of diarrhea in twenty foals of from two to 75 days of age. Thirteen of these foals had severe clinical signs of disease for more than four days, and eight had received treatment with other antimicrobials, including neomycin and streptomycin. All animals were given 250 mg gentamicin IV twice daily until remission of the clinical signs of disease, even though no bacteriological typing of the cause of the diarrhea was attempted. The IV route was selected over the oral route because of the poor absorption of gentamicin from the gastrointestinal tract and the signs of systemic involvement in many of these foals. In all foals, remission, as evidenced by improved stool consistency, had occurred within 60 hours of starting therapy, and in some foals had occurred after only one day of therapy. Signs of improved appetite and elimination of dehydration and depression occurred in most of these animals within 24 hours of starting treatment, and body temperature also declined to normal within 36 hours. No recurrence of diarrhea in any animal was observed during a post-treatment period of 14 days. Hamm and Jones suggested that these very promising results would justify a more thorough study of the efficacy of gentamicin in the therapy of foal diarrhea.

While these results are impressive, experience in Kentucky suggests that gentamicin should be used with particular care in young foals, as renal function in these animals may not be mature enough to withstand prolonged gentamicin therapy. In one series of 14-day-old pony foals which received high doses of gentamicin for seven to 10 days to control diarrhea, good control of the diarrhea was obtained. However, five to six weeks later a number of these foals became lethargic, showed ventral edema and died of renal failure. Postmortem examination showed signs of proximal tubular damage, and similar patterns of proximal tubular damage with a history of gentamicin therapy a number of weeks previously have been seen in foal accessions to our postmortem room at UK. It is probably wise, therefore, to use gentamicin sparingly in young foals and not to prolong therapy unduly. Treatment with other drugs which are either nephrotoxic or which are excreted via the kidney is also likely best avoided in young horses on gentamicin therapy.

Kanamycin has broad antibacterial activity against gram-negative pathogens, but is not effective against Pseudomonas, and some E. coli and Klebsiella are resistant. Experience in human medicine suggests that though Shigella, Salmonella and Staphylococcus may be sensitive to kanamycin in vitro, they respond poorly in vivo to this drug. Because kanamycin, like all aminoglycosides, is concentrated in the urinary tract and is very active in an alkaline urine, it has a valuable role to play in the treatment of urinary tract infections. In general, however, since kanamycin is less active on a molar basis than gentamicin and is more toxic, gentamicin is now the drug of choice for cases in which kanamycin was previously used. Figure 3 shows

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*Dr. T. W. Swerczek. Personal communication, University of Kentucky
plasma levels of kanamycin after 10 mg/kg IV. After IV injection, kanamycin has a plasma half-life in the horse of about 90 minutes, and Bogg et al. has estimated that tissue levels after this dose peak at about 30 µg/ml. This value is in good agreement with data of Knight et al. which suggests peak serum levels of gentamicin of about 20 µg/ml after 5 mg/kg IM in horses, and recommends use of this dose three times a day to maintain plasma levels of kanamycin.

Neomycin is closely related to kanamycin but is even more toxic, which limits its usefulness. In human medicine it is rarely used systemically because of its toxicity. Neomycin is principally used, therefore, as a topical preparation for infections of the eyes, ears, and skin, and to "sterilize" the bowel prior to surgery. Neomycin has been suggested for systemic use in the horse along with ampicillin in the treatment of contagious equine metritis, but its role and efficacy in this therapy remains to be determined.

Amikacin is a recently developed aminoglycoside antibiotic, whose principal advantage is that the majority of gentamicin- and kanamycin-resistant Enterobacteriaceae are presently susceptible to it. Amikacin is thus an antibiotic which is currently best held in reserve and only used under special circumstances. Dosage data for this drug in the horse is not available but provisional data from humans suggests dosages of about 7.5 mg/kg every eight hours.

Tobramycin is another aminoglycoside which closely resembles gentamicin in its antibacterial spectrum and pharmacology. In general, Pseudomonas spp. are likely to be more susceptible to tobramycin than gentamicin, but E. coli are likely to be more resistant. Sisomycin and netilmicin are two other recently developed aminoglycosides, both again with little apparent advantage over gentamicin.

Spectinomycin is an aminocyclitol antibiotic rather than an aminoglycoside, and thus its actions and toxicities differ substantially from those of a typical aminoglycoside. It is less active on a molar basis than this group of drugs, and data from humans suggest dosage rates of up to 40 mg/kg parenterally. It has been used in the horse with good results as an intravenous infusion in the treatment of mixed uterine infections and infections due to Klebsiella. When administered in this way the dose to an adult horse is about 2 to 3 g of spectinomycin in 500-ml volume of three to four days. Because spectinomycin is not an aminoglycoside, it can be used in high doses without fear of inducing eighth nerve damage or renal toxicity. Adverse reactions reported in humans include dizziness, vertigo, malaise, and anorexia. Spectinomycin may also be used parenterally in the horse and dosage schedules and indications for its use by this route in the horse are now being worked out.

In summary, gentamicin is clearly the aminoglycoside of choice in the therapy of most gram-negative infections in horses. It is currently effective against a wide range of gram-negative organisms, and in combination with carbencillin, is especially useful in treating deep-seated infections due to Pseudomonas spp. Gentamicin should, however, be used with care in young foals, and all horses on gentamicin should be watched carefully for signs of renal damage. Gentamicin has essentially replaced kanamycin in equine medicine and relegated streptomycin to use in penicillin-streptomycin combinations. While a number of new aminoglycoside antibiotics have recently been developed, these, with the possible exception of amikacin and spectinomycin, have not been able to show apparent advantages over gentamicin.

References
Viewpoints

Studies in Equine Biomechanics

James R. Rooney, D.V.M.

While this article is in the nature of an editorial, it is directly related to the general concerns of our series on mechanics and lameness. As one follows the literature of equine medicine and surgery, it becomes clear that most articles are prepared by veterinarians in academic settings. The rare article by a practicing veterinarian is usually a case report involving an unusual and, therefore, interesting, single case.

In general, I have no objection to such articles (though I object to many, particularly surgical papers, specifically). There is a type of article rarely seen, however, which I sorely miss. Let me give an example: one practitioner of my acquaintance has been keeping records of all the cases of bowed tendon encountered in his practice for many years. He has a wealth of epidemiological information in those records which should be collated, studied, and published. Other practitioners have similar data on other conditions or could, with little effort, keep running records of such data for a variety of entities: pulled suspensory, ringbone, spavin, navicular disease, whatever. It is certainly true that most practitioners could keep such records, and equally true that most have neither the time, training, nor inclination to collate and study such information.

The suggestion I make is that academics could, in collaboration with a trained epidemiologist and a given number of practicing veterinarians, develop and implement an epidemiological recording system. As the practitioners accumulated the data the academics could evaluate it with the guidance of the epidemiologist and the assistance of computing facilities.

Such studies, taking advantage of the enormous volume of material seen by practicing veterinarians, could provide a wealth of information for the practitioners themselves as well as essential guidelines for more strictly research-type studies. The cost of experimentally derived information on lameness is enormous and, in some 20 years in the business, I have seen little evidence that horsemen and the horse industry will support such work to any significant degree. While experimentally derived information may be the “best” information (though I am prepared to debate the point), field experiences and observations, if properly collected and evaluated, are much less expensive and may, indeed, point with great clarity to the precise experimental study necessary to answer a specific point or clear up a particular lameness problem. Too often the research study simply reflects the current interest of the researcher and does not take into account the “real-life” situation which, after all, is where research results must eventually prove themselves.

I believe many equine practitioners would be willing to cooperate in such endeavors if brought into the initial planning of the study. It is all too easy for us nonpracticing eggheads to develop elaborate recordkeeping systems for someone else to struggle with. In fact, the study would be collaborative, with the practitioner’s role and understanding of the project as essential as that of the collarist.

The official veterinarians at racetracks and shows, as well as private practitioners, all have much to give to such studies for the benefit of themselves, clients, horse organizations and to knowledge in veterinary medicine in general. There is a vast untapped resource in the experience and observational capabilities of the practicing veterinarian and, so far as I am concerned, it is past time to begin tapping that resource. Is anyone interested?

Bryans Honored With Degree

Dr. John T. Bryans, University of Kentucky professor of veterinary science, was presented an honorary degree of doctor of veterinary medicine last month by the University of Berne in Switzerland.

Bryans developed a blood test to detect venereal disease in horses, and a vaccine to prevent virus abortion in mares, both of which contributed to the horse industry worldwide. The Berne citation recognized his contributions toward control of infectious diseases in horses, and his encouragement of an international information exchange on horse diseases.

Under Bryans’ leadership there have been four international conferences: in Italy in 1966, and in France in 1968, 1972 and 1977.

A native of New Jersey, Bryans has been at University of Kentucky since 1954. He spent a sabbatical at Berne in 1969 studying horse infectious diseases.