The Aminoglycoside Antibiotics: A Guide To Therapy

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PREFACE

The aminoglycoside antibiotics have had a prominent role in the treatment of bacterial infections since streptomycin became available for clinical use in 1947. The continued interest in the application of these antibiotics has provided the stimulus for preparation of this Uniscience volume. Over the years, a prodigious number of scientific publications have appeared in the world’s literature pertaining to one aspect or another of the aminoglycoside antibiotics. Much of the pertinent literature that is appropriate to the needs of the clinician and laboratory scientist is scattered throughout a vast array of scientific journals, books, and other publications.

In an effort to compile a concise overview of topics consistent with the objectives of the editors and in order to provide an adequate bibliography for those readers requiring more detailed information, the following topics have been included: the chemistry and structural relationships, mechanisms of action and resistance, pharmacokinetics, therapeutic uses, toxicity, problems of susceptibility testing, and available serum assay methodologies. Because the most frequently utilized aminoglycosides are gentamicin, tobramycin, and amikacin, most of the material included pertains to these three antibiotics. It has not been the intent to provide a complete encyclopedic treatise on all individual topics due to space limitations of a publication this size.

The editors are indebted to the diligent efforts of all the contributors. Their cooperation in sharing their ideas, expertise, and valuable time has been instrumental in the successful completion of this work.

It is our hope that the readers will find The Aminoglycoside Antibiotics: A Guide to Therapy of value in providing a better understanding of the role of these agents in the treatment of infectious diseases and to further provide a means for eliminating or preventing potential problems that may occur with their therapeutic use.

W. G. Barnes
G. R. Hodges
DEDICATION

Thorkil Jensen, Ph.D., for the guidance I received during my graduate training in microbiology and for demonstrating uncompromising principles as a teacher, researcher, and administrator.

Alex C. Sonnenwirth, Ph.D., whose contributions and relentless efforts to improve the field of clinical microbiology have been a continual source of encouragement and inspiration to other microbiologists.

W.G.B.

This volume is dedicated to Robert L. Perkins, M.D., and the late Samuel Saslaw, M.D., for nurturing my interest in infectious diseases.

G.R.H.
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I. AMINOGLYCOSIDE ANTIBIOTICS

A. Definition

Aminoglycoside antibiotics are a group of closely related basic carbohydrates. They consist of an aminocyclitol ring connected in glycosidic linkage to one or more aminosugars. The amine groups that are present can form crystalline salts with acids.

B. General Structural Units

1. Aminocyclitol

The aminoglycoside antibiotics are characterized by the inclusion of an aminocyclitol group in their structure. An aminocyclitol group may be defined as a saturated ring with amine and hydroxyl substitutions. In fact, Rinehart has suggested that the term aminocyclitol be used to describe this group of antibiotics rather than the less precise term, aminoglycoside. While many variations are possible, the basic aminocyclitol group found in the clinically useful antibiotics is streptamine.

![Streptamine](image1)

The particular streptamine that is usually included in the structures of these antibiotics is actually 2-deoxystreptamine.

![2-Deoxystreptamine](image2)

This compound possesses two cis amino groups at positions 1 and 3. The 2-deoxy portion of the name indicates the absence of a hydroxyl group at position 2.

Guanidine has the following structure:
If the amine functions of the streptamines are part of a guanidine group, the molecule is referred to as a streptidine.

Streptomycin is the only antibiotic of clinical importance that contains the streptidine group.

2. Aminosugars

Aminoglycoside antibiotics are also characterized by aminosugars attached to the aminocyclitol ring in glycosidic linkage. The aminocyclitol, 2-deoxystreptamine, contains three hydroxyl groups at C4, C5, and C6. These are available for combination with a sugar in glycosidic linkage. Aminosugars are particularly important in this regard. An example of such a sugar may be found in 2,6-diaminoglucose.
If we combine this sugar with 2-deoxystreptamine in glycosidic linkage, the following product results:

![Diagram of Neamine (Neomycin A)](image)

The above substance is called neamine or neomycin A. A glycoside can also be formed at C₅ of the 2-deoxystreptamine ring. Destomycin A is an example of such a compound.

![Diagram of Destomycin A](image)

A very large and important group of aminoglycoside antibiotics are the 4,5-disubstituted 2-deoxystreptamine derivatives. Neomycin C is an example of this group.

![Diagram of Neomycin C](image)

Another very important group is the 4,6-disubstituted 2-deoxystreptamine derivatives. Kanamycin A is an example of this group.
Before further discussion of specific drugs, a word about nomenclature is in order. The basic group of the aminoglycoside antibiotics is the 2-deoxystreptamine ring. It is numbered as shown in Figure 2. The aminosugars are numbered in the customary manner. In the case of the aminoglycoside antibiotics, the sugar attached to the C4 of the aminocyclitol ring is numbered with numbers designated as prime numbers. This is illustrated in Figure 5. The second sugar that is attached to the aminocyclitol ring is numbered with double prime numbers. A third sugar that occurs in the molecule is numbered with triple prime numbers. Please refer to neomycin C (see Figure 8) for a specific example of numbering the aminoglycoside antibiotics.

C. Specific Aminoglycoside Antibiotics

1. 4,6-Disubstituted Aminocyclitols

a. Kanamycin

Kanamycin is an example of a 4,6-disubstituted aminocyclitol. It contains two sugars which are attached to positions 4 and 6 of a typical 2-deoxystreptamine ring. The aminosugar attached to position 6 is kanosamine (3-glucosamine). The aminosugar attached to position 4 may vary. This gives rise to three kanamycins which are called kanamycin A, kanamycin B, and kanamycin C. The official product is kanamycin A (see Figure 9).

Kanamycin B is one of the kanamycins.
Kanamycin C represents the third member of the group.

Kanamycin B has in its structure a neosamine (2,6-diaminoglucose). It is about twice as potent as kanamycin A, which is a 6-aminoglucose derivative. Kanamycin A, in turn, is two to four times more potent than kanamycin C. Kanamycin C is the glucosamine (2-aminoglucose) analogue.

Substitutions on the amines which decrease the basicity of the amines decrease the antibiotic activity. For example, if the amines are acetylated and their basicity is destroyed, the activity is reduced or eliminated. If kanamycin A is acetylated at C6, the product is inactive. The basicity of the ring has been destroyed. If kanamycin B is acetylated at C6, the product retains a reasonable amount of activity. The basicity of the ring has not been destroyed because there is still an amino group at C6. The activity is similar to that exhibited by kanamycin C, which has its basic amine at C2.

It may be concluded that the sugar at the 4 position of the aminocyclitol must have at least one amino group to be biologically active. The derivatives may be listed as follows in the decreasing order of potency:

2',6'-diamino > 6'-amino > 2'-amino > hydroxyl

These kanamycin derivatives are metabolized by phosphorylation at C3 and adenylation at C4. Removal of the hydroxyl groups at C3 and C4 should lead to derivatives that resist such chemical changes. Tobramycin and dibekacin are examples of such modifications.

b. Tobramycin

Replacement of the hydroxyl groups on the aminosugar ring with hydrogen atoms leads to an increased antibiotic potency in the kanamycin B series. Tobramycin is an example of such a change. It is a 3'-deoxy derivative of kanamycin B, and it shows an increased potency over kanamycin B.
c. Dibekacin

Replacement of both the 3'- and 4'-hydroxyl groups of kanamycin B gives another more active compound called dibekacin. It is also referred to as dideoxykanamycin B or DKB.

These compounds are examples of the increased antibiotic activity when the hydroxyl groups at 3' and 4' are replaced with a hydrogen substitution. The same effect is seen in the kanamycin A series. Increased potency is observed with the 3'-deoxy and the 4'-deoxy derivatives of kanamycin A.\(^4,5\)

However, some modifications decrease the antibiotic activity in this series. Replacement of the 3'- and 4'-hydroxyl groups with a methoxyl or amino group caused a lessening of activity.\(^6,8\) Unsaturation of the aminosugar ring has a variable effect. Replacement of the 3',4' hydroxyl groups with a double bond decreases the activity. However, a double bond between carbons 4' and 5' increases the activity. This might be due to the alteration of the ring's conformation due to the double bonds.\(^9\)

Modification of the kanosamine ring of kanamycin A has little or no effect. The C\(_6\)-chloro kanosamine and the C\(_6\)-deoxy kanosamine have essentially the same activity as the parent kanamycin A.\(^10,11\)
d. Gentamicin

Gentamicin is also an antibiotic complex of the 4,6-disubstituted aminocyclitol series. Various species of *Streptomyces* have provided almost all of the antibiotics in this series, with the notable exception of the gentamicins which are produced by species of *Micromonospora*.

Gentamicins have three main components. These components are referred to as gentamicins C1, C2, and C1A. Thirteen other gentamicins have also been reported. The gentamicin components C1, C2, and C1A have the following structural relationships:

![Structural diagram of gentamicin components](image)

The gentamicins are similar to the kanamycins in two respects. They are derivatives of a 4,6-disubstituted aminocyclitol. The substitutions at positions 4 and 6 are aminosugars. They are different from the kanamycins in the nature of the sugar residues that are substituted. The aminosugar at C4 is a 2,6-diamine derivative. There are no hydroxyl groups at C3 and C4. In the kanamycin series, kanamycin B is the most active, and it has a 2,6-diaminosugar. Replacement of the hydroxyl groups at C3 and C4 gives tobramycin and dideoxy-kanamycin B, both of which have increased activity over the parent kanamycin. In this series of gentamicins, the C6 and the amine group on the C6 carbon is substituted with a methyl group with the retention of good activity.

The sugar at C6 of the aminocyclitol ring contains a hydroxyl group at C2. If this group is removed or methylated, the activity is decreased. Activity is retained if this hydroxyl group is replaced with an amino group.12 The C3 amino group is a secondary amine. The primary amine analogue is also active. The hydroxyl group at C4 can be methylated with the retention of activity. The C6 deoxy and the C6 chloro derivatives also are active.10,11

e. Sisomicin

Sisomicin is another example of changes in the aminosugar portion of the molecule.
These modifications are made in the antibiotics of the gentamicin series. The aminosugar in sisomicin is an unsaturated diaminosugar. The amines are at C$_2$ and C$_6$ of the sugar. This combination seems to be very favorable in the kanamycin series (q.v.). In addition, the hydroxyl groups at C$_3$ and C$_4$ have been removed. This was seen to be very beneficial in the debekacin series (q.v.). Introduction of a double bond between the C$_4$ and C$_5$ positions has previously been stated to increase the activity. This combination of changes increases the activity over gentamicin.$^{13}$

**f. 5-Episomicin**

A further change in the molecule of sisomicin gives the isomer called 5-episisomicin. This product is a semisynthetic variation of sisomicin where the C$_3$ hydroxyl group has been epimerized.
The resulting product has a spectrum and potency similar to gentamicin with an increased potency against certain species of organisms. Epimerization of the sisomicin hydroxyl at C₅ produces a molecule that is resistant to enzymatic inactivation. Even though the hydroxyl group at C₅ is not a site of enzymatic attack, the change in the orientation of this hydroxyl group protects the molecule against enzymatic attack upon other sites in the molecule.¹⁴

2. Derivatives of 4,6-Disubstituted Aminocyclitols

a. Amikacin

The most important modification that has been made on the aminocyclitol ring is the substitution on the amine on the C₁ carbon atom.

Amikacin is basically a kanamycin A structure (see Figure 9) that has been synthetically modified by acylation of the amine at C₁ with 2-hydroxy-4-aminobutyric acid (HABA). This increases the activity markedly. It has been proposed that this amine group at C₁ is active in the binding of the antibiotic to inactivating enzymes, and the HABA hinders this binding.¹⁵ In addition, the stereochemistry of this acid (HABA) is quite important. Acylation of the aminocyclitol with the S isomer of HABA gives a product that is four times more potent than acylation with the R isomer.
Amikacin is an illustration of this beneficial acylation with HABA.

![Amikacin](image1)

FIGURE 19.

However, all modifications of the amine group at C1 of the aminocyclitol ring are not equally favorable. Corresponding acylation of the aminocyclitol with 4-aminobutyric acid or 2-hydroxybutyric acid gives compounds that are almost inactive. Activity is reduced if the length of the chain is increased or shortened. Activity is greatly reduced if either the hydroxyl or amine group is eliminated. Other modifications of the acyl group are only weakly active.16

b. Butikacin

Butikacin is a compound with a 2-hydroxy-4-aminobutyl substitution on the amine at C1. It is not an amide-like amikacin. However, the absolute configuration of the butyl substitution is S which is the same as that seen in amikacin. Butikacin possess an antibiotic activity similar to amikacin or kanamycin A against the aminoglycoside-susceptible bacteria. Like amikacin, it is highly active against aminoglycoside-resistant bacteria.17

![Butikacin](image2)

FIGURE 20.
c. Propikacin
Another active variation with a substitution on the amine is propikacin. The substitution is an isopropyl group that has two hydroxyl groups. Either of these hydroxyl groups is on a carbon that corresponds to the position of the alcohol group in the highly active HABA series. The antibiotic activity of propikacin is similar to that of amikacin.18

![](image)

**FIGURE 21.**

d. Netilmicin
Netilmicin (1-ethylsisomicin) is an active compound with a simple ethyl group on the amine at C₁. It has antibacterial activity similar to the related sisomicin, but also can resist enzymatic inactivation.19

![](image)

**FIGURE 22.**

3. 4,5-Disubstituted Aminocyclitols
a. Neomycins
This series of antibiotics possesses the typical deoxystreptamine ring. This ring is substituted with aminosugars at positions 4 and 5. Neomycin A was discussed previously. It is also referred to as neamine.
This product is actually a degradation product obtained from neomycin B and neomycin C. Neomycin B and neomycin C are isomers that differ in the orientation of the substitutions on the terminal sugar residue at position 5.
The commercial preparation neomycin consists mainly of neomycin B. The presence of a fourth aminocarbohydrate ring such as that found in neomycin B or neomycin C increases the antibiotic potency severalfold. Neomycin is much more potent than ribostamycin which is the corresponding antibiotic without the fourth aminocarbohydrate ring.

Modifications of the D-ribose moiety within the neomycin molecule have produced compounds with variable antibacterial activities. However, when an aminosugar is attached to this D-ribose group, a marked increase in activity is observed. The neomycin series is an example.

**b. Paromomycin**

The paromomycin series is analogous to the neomycin series. The paromomycins have a D-glucosamine residue attached to the C₄ hydroxyl group of the deoxystreptamine. The neomycins have neosamine C (2,6-diaminoglucose) residue attached to the C₄ hydroxyl group of the deoxystreptamine. The other sugar residues are the same.

Paromamine contains a single sugar, D-glucosamine, attached to the deoxystreptamine residue. Neomycin A is the analogous product with a single sugar, neosamine C, attached to the deoxystreptamine residue. Paromamine has been referred to as neomycin D.

Paromomycin I and paromomycin II are also related to neomycin B and neomycin C by having a 2-aminoglucose (D-glucosamine) residue attached to the corresponding position of the deoxystreptamine instead of the 2,6-diaminoglucose (neosamine C) group.
Because of the similarities in structures, the compounds are similar in antibiotic potencies.

c. Lividomycins

Lividomycin A and lividomycin B are antibiotics related to the paromomycins.

The paromomycins have a hydroxyl group at C₃, whereas the lividomycins are desoxy analogues. In addition, lividomycin A has an additional sugar residue in its structure. Removal of the C₃ oxygen function has previously been shown to increase the antibiotic activity of the molecule. The potency of the lividomycins is equal to or greater than neomycin or kanamycin.⁴²

4. Derivatives of 4,5-Disubstituted Aminocyclitols

a. Butirosin

As noted before, acylation of the amino group in the deoxystreptamine ring can markedly increase the antibiotic activity. The 2-hydroxy-4-aminobutyric residue (HABA) seems the most favorable substitution. This synthetic modification has been made in the butirosin series. This series is similar to ribostamycin which was previously discussed.
The introduction of the 2-hydroxy-4-aminobutyryl group favorably affects the activity of the parent molecule in the same way that is seen in the conversion of kanamycin A to amikacin which was previously discussed.

5. Guanidine Derivatives of Aminocyclitols
   a. Streptomycin

When streptomycin was discovered by Schatz et al. in 1944, it represented the first of a new class of antibiotic substances that was referred to as the aminoglycoside antibiotics. Streptomycin has the following structure:
The previously discussed aminocyclitol derivatives contained a 2-deoxystreptamine ring as an integral part of their structure. In this series the 2-deoxystreptamine is replaced with a streptidine ring.

![2-Deoxystreptamine](image1)

![Streptidine](image2)

**FIGURE 29.**

The two rings are very similar. The guanidine group and the amine group are both basic substituents. Both of the basic functions are located in the 1,3 position, and they are both located cis to each other. The streptidine ring does have an alcoholic group which is absent in the 2-deoxystreptamine derivative. The other alcoholic hydroxyl groups are present at C₄, C₅, and C₆ in both series. Their orientation is the same in both series.

In the streptomycin series, two sugars are attached to the streptidine ring. The first sugar (L-streptose) is attached to position 4 of the streptidine ring. The second sugar (N-methyl-L-glucosamine) is attached to position 2' of the L-streptose residue. The alcoholic hydroxyl groups at positions 3", 4", and 6" are unsubstituted.

The principal modifications of the streptomycin antibiotic have been made on the L-streptose ring. The aldehyde group has been reduced to the corresponding alcohol group. The dihydrostreptomycin so obtained has an activity similar to the original streptomycin. However, conversion of the aldehyde group to the corresponding methyl group produced a derivative that was only 10% as active. Oxidation of the aldehyde group to the corresponding acid produced a compound of low activity. Condensation of the aldehyde with nitromethane and subsequent reduction of the nitro group gave the following compounds which had a poor activity.

![L-Streptose Modifications](image3)

**FIGURE 30.**
Modifications of the $N$-methyl-$L$-glucosamine were basically unsuccessful. Conversion of this sugar to the corresponding primary amine and tertiary amine produced compounds with weak activity or no activity.\textsuperscript{27}

6. Miscellaneous Aminoglycoside Antibiotics

a. Apramycin

This antibiotic was originally a portion of the nebramycin complex. This complex consisted of seven factors. Factors 2 and 6 were the best. Factor 6 is the same as tobramycin which has already been discussed. Factor 2 is called apramycin.

![Structure of apramycin](image)

At first glance, the structure of apramycin seems quite different from the previously discussed aminoglycoside antibiotics. However, in reality, it is really quite similar. Apramycin contains the typical 2-deoxystreptamine group. The orientation of the amine groups and the hydroxyl groups are exactly the same as in the other derivatives that have been previously discussed. Like the other derivatives, the 2-deoxystreptamine ring is substituted at the C$_4$ position. Rather than substitution with a simple monosaccharide, the 2-deoxystreptamine is substituted with an amine-substituted octose dialdehyde. When this sugar forms a typical hemiacetal derivative, the following structure is formed:

![Octose Dialdehyde](image)  
![Cyclized Octose Dialdehyde](image)
This bicyclic residue comprises the central part of the apramycin structure. Attached to this residue is a 4-aminoglucose fragment. Apramycin shares the 2-deoxystreptamine and the aminosugars that are seen in other aminoglycoside antibiotics. The bicyclic aminooctose dialdehyde is a bit more complex than groups in previously discussed derivatives, but it is qualitatively very similar to these derivatives. Apramycin possesses a good antibiotic activity that is about equal to gentamicin.28,29

b. Spectinomycin

Spectinomycin is also known by the name actinospectacin. It is an aminocyclitol antibiotic of a rather unusual structure.

It is similar to the previously discussed aminoglycoside antibiotics in regard to mechanism of action and bacterial spectrum.

Ring A resembles the streptamine residue that is commonly seen in previously discussed aminoglycoside antibiotics. It is attached by means of glycosidic linkage to ring C. Some modifications of its structure have been reported. These involve reduction of the ketone at C4. Both of the epimeric alcohols so produced were less active than the parent ketone. Epimerization of the alcohol at C7 also gave a compound that showed a loss of antibiotic activity.30-32

II. SUMMARY

The aminoglycoside antibiotics are very closely related. They possess a 1,3-diaminocyclohexitol as an integral part of their structure. The two amino groups are cis oriented at the C1 and C3 positions. It is usually more favorable if the aminocyclitol ring is a deoxy derivative with no oxygen function at C2 (e.g., deoxystreptamine). If the amine group at C4 of the aminocyclitol ring is substituted, such as acylation, a compound with increased activity is produced. This substitution is thought to hinder the attachment of the molecule to inactivating enzymes and consequently give a product with greater activity.

An aminosugar is also an important part of this molecule and is necessary for antibiotic activity. These sugars are glycosidically attached to the hydroxyl groups of the aminocyclitol at C4, C5, or C6. An aminosugar (e.g., an aminoglucose) is commonly attached to C4 of the aminocyclitol ring. This aminosugar may have two amino groups (e.g., 2,6-diaminoglucose) and should have at least one amine substitution (e.g., 2-glucosamine). Variations of the aminosugars in the parent molecule can affect the antibiotic activity. The 2,6-diaminoglucose derivatives are more active than the 2-aminoglucose derivatives in the kanamycin series for example.

At another of the hydroxyl groups of the aminocyclohexitol ring, an additional sugar or sugars can be attached (e.g., neomycin). These sugars can increase the antibiotic activity of the molecule significantly.
The deoxyglucose derivatives of the aminoglucone portion of the molecule are more active than their oxygenated analogues. The aminoglucone ring might have two hydroxyl groups (e.g., the neosamine C residue in kanamycin B). If these hydroxyl groups are removed such as in tobramycin or dibekacin, the antibiotic activity is increased markedly.

While the aminoglycoside antibiotics are effective against both Gram-positive and Gram-negative organisms, their main value is their use against Gram-negative organisms. This is because many other orally active antibiotics are effective against Gram-positive organisms. The use of the aminoglycoside antibiotics is thus limited in practice to the Gram-negative infections. To overcome this limitation, it would be desirable to have an orally active aminoglycoside antibiotic.

To accomplish this, one might make a pro-drug. The aminoglycoside antibiotics are highly water soluble. Acylation of some of the hydroxyl groups with fat-soluble substituents would decrease the water solubility and possibly increase intestinal absorption of the orally administered drug. Hydrolysis of the acyl group in the body would regenerate the parent aminoglycoside antibiotic. The compounds might be made orally active in this way.

Synthetic alterations of the aminoglycoside antibiotics might produce derivatives with a lower toxicity (e.g., ototoxicity). Further work might also provide derivatives that are effective where the R factor is involved. The full potential of the aminoglycoside antibiotics has not yet been realized.
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