An Illustrated Review About Aminoglycosides

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Abstract

Aminoglycoside is a potent antibiotic that stops the protein synthesis continuation by binding to the ribosomal decoding site. They are used to treat infection caused by the aerobic, gram-negative and certain gram-positive organisms. The most commonly used aminoglycoside is Gentamicin. Generally, single daily dosing of aminoglycosides is appeared to be safer, cost effective and efficacious. Prolonged use of the drugs will lead to side effects such as ototoxicity and nephrotoxicity. Resistance towards aminoglycoside is possible but it rarely happens. The structures activity relationship (SAR) of some aminoglycoside antibiotics is further reviewed in this paper.

Introduction

Aminoglycoside has been found 50 years ago and because of their excellent attainment, it was still used as a drug of choice to give various functions including rapid concentration-dependent bactericidal effect, synergism with beta-lactam antibiotics, clinical effectiveness, a low rate of true resistance and it is also low cost [1].

The first aminoglycoside found, streptomycin, was isolated from Streptomyces griseus in the year 1943 [2]. On the other hand, aminoglycosides that was usually given topically, neomycin, was isolated from Streptomyces fradiae, had better activity than streptomycin against aerobic gram-negative bacilli [2]. Gentamicin, was isolated from Micromonospora in the year 1963, was a breakthrough in the treatment of gram-negative bacillary infections, including those caused by Pseudomonas aeruginosa [2].

The aminoglycosides remain drugs of choice in treating many diseases including septicaemia, serious infections due to Gram negative bacilli, and bacterial endocarditis [1]. Streptomycin, the earliest aminoglycosides found, is used to treat infections like tuberculosis, plague, brucellosis, and tularemia. Tobramycin is used to treat serious bacterial infections caused by susceptible strains in lower respiratory tract which is an infection caused by bacteria P. Aerugionosa, Enterobater sp, E. Coli, Klebsiella sp, and S. Aureus [3]. Amikacin Sulphate Injection, USP is indicated in the short-term treatment of serious infections due to susceptible strains of gram-negative bacteria, including Pseudomonas sp, E. Coli, species of indole negative and indole positive Proteus, Providencia sp, Klebsiella-Enterobacter-Serratia sp, and Actinobacter sp. [4]

Classification and SAR of Aminoglycoside Antibiotics

Natural aminoglycoside antibiotics share a non-sugar 2-deoxystreptamine scaffold connected to amino sugar substituents at the 4-, 5- and 6-positions. The two most important classes of aminoglycoside antibiotics are the 4, 5- and 4, 6-disubstituted 2-deoxystreptamine derivatives. [5] The 4, 5-disubstituted 2-deoxystreptamine compounds include neomycin B whereas the 4,6-disubstituted 2-deoxystreptamine derivatives include gentamycin, kanamycin and streptomycin. Aminoglycoside antibiotics of these three groups, 4, 5- and 4, 6-disubstituted 2-DOS derivatives and apramycin, share in common a target site at the decoding center (A-site) of bacterial 16S ribosomal RNA (rRNA). 2-deoxystreptamine scaffold is the key pharmacophore required for the precise anchoring of the drugs at the RNA target. [6]

1. Streptomycin

Streptomycin is the first aminoglycoside antibiotic to be discovered and was the first antibiotic to be used in treatment of tuberculosis. It was discovered in 1943, in the laboratory of Selman Waksman at Rutgers University. Streptomycin is derived from the bacterium Streptomyces griseus. It inhibits bacterial growth by inhibiting protein synthesis. Specifically, it binds to the 16S rRNA of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit. It is chemically stable and rapidly bactericidal, with a broad spectrum of inhibitory activity (apart from anaerobic bacteria). [7] Streptose, the central moiety, is a C-3-formyl derivative of 5-deoxy-Llyxose. [8] Two major precursors of the streptidine portion of the molecule have now been defined, n-arginine and n-glucose (1, 2). [9]

2. Neomycin

Neomycin, an aminoglycoside antibiotic, discovered on 1949 in the lab of Selman Waksman. It has excellent activity against gram-negative bacteria, and has partial activity against gram-positive bacteria. It is produced naturally by the bacterium Streptomyces...
fradiae. Most potent aminoglycoside translation inhibitors [10].

3. Kanamycin
Kanamycin is made up of 3 rings. Ring II is sugar group, while ring I and III are non-sugar group. Kanamycin B is a more potent antibiotic than either kanamycins A or C. The presence of a diamino hexose, therefore, results in a compound that is a better inhibitor of protein synthesis than one containing only one amino group. Therefore, when only one amino group is present, an antibiotic that contains a 6-amino substituent is more active than one containing a 2-amino substituent. Antibiotic activity can be related to the number and location of amino groups in the hexose moiety glycosidically linked to the 4-position of deoxystreptamine as follows (in decreasing order of potency): 2', 6'-diamino > 6'-amino > 2'-amino > no amino

4. Gentamicin
There are 3 types of gentamicin in this class of aminoglycosides such as Gentamicin C1, Gentamicin C2 and Gentamicin C1a. Gentamicin C1 exists when both R1 and R2 are CH3. Gentamicin C2 exists when R1 is CH3 and R2 is H. Gentamicin C1a exists when both R1 and R2 are H. The structure of gentamicin is consistent with the aminoglycoside structural activity relationship (SAR), except few minor changes. Gentamicin C1a binds in the major groove of the RNA.

Discussion

Illustration is a very useful method in explaining a particular matter with the use of only limited words. Images also produce a longer memory in our mind and it leads to the reason why we prefer to do an illustrated review on this topic.

In the beginning of our review, an illustration is used to explain the general uses of aminoglycosides and it shows exactly where the drugs should be applied to. Besides, several illustrations and structures have been used to illustrate the mechanism of action of aminoglycosides on the ribosomal subunit. This is to provide a more vivid idea on how a drug attaches to the specific part of the ribosomes and render the production of non-functional protein which eventually becomes detrimental to the bacteria. We also resort to the presentation of information in table form. It enables us to compare and contrast the spectrum of activity, clinical indication, pharmacokinetic and side effects of different types of aminoglycosides. By presenting all the information in a table, similarities and differences among them are more obvious as compared to explaining them in separate way. For examples, it is obviously depicted in the table that aminoglycosides are effective against both gram positive and gram negative bacteria.

Our visual memory is much more powerful than our audio memory. Converting a whole page of notes into pictures or illustrations ensures that we understand the information, we are summarising it and converting it into a picture. It will be so much easier to recall this picture from memory during an exam than to recall every word on a page of text. Using coloured pictures or illustrations to focus on main part of chemical structures stimulates our mind to remember the structure very well and its specifications. It acts as an instant guide for pharmacy students to read thoroughly and understand quickly during last minute revision or final preparations to avoid wasting time reading notes in a long essay form.

A structure with illustration used in explaining the structure relationship activity of aminoglycoside not only can facilitate the conceptualization and dissemination of information through it, but also motivate students to read it. With the important points fitted into each part of structure, it can help the students to interpret the structure more easily. They must be related to the text content with the structure of aminoglycoside because it is the nature of illustrations. As a result, they can know clearly about the function of each part of structure rather than when we separate the point with the structure. This is because it will make them confused and it is more difficult to relate the text content with the structure. It is a tedious task for them to find out the points that correspond for each part of drug structure. This is correlated with research done by Russell N. Carney which stated that illustration improve students’ learning from text because they make the text more concentrated, concrete, coherent, comprehensible, correspondent and codable [19]. An illustration form of drug structure can have representation and interpretation function. The more difficult the text is to be understood, the more the illustration helps.

For an illustrated article, a striking colour also plays a major role in helping the reader to recall facts and information. As compared to the black and white sentences or diagrams, the coloured one will make it easier for someone to focus on what they have to memorize and vice versa. Normally we use a striking colour such as red and yellow to emphasize the keywords or main points and we are likely to retain the information and remember them better. Colour tends to be processed by the right side of the brain and by introducing the colour into the information, it will stimulate more of your brain than if you just using one colour. By using colour, it makes the article far more
interesting to look at, therefore much more engaging to the emotions and stimulates senses at the same time. Coloured diagrams, tables or explanations are important especially if you are doing a tedious or difficult topic.

In our opinions, we think that aminoglycosides are very useful in fighting a wide range of disease-causing bacteria. In reality, they have been to treat urinary tract infection caused by E. coli and other bacteria. Furthermore, Streptomycin is being used as a first line agent in treating Tuberculosis disease which is caused by the Mycobacterium Tuberculosis. Most of them are given as intramuscular and intravenous injections. The only drug that can be taken orally in this class is the Neomycin due to its high toxicity if given parenterally. All members of aminoglycoside family of drugs can be ototoxic and nephrotoxic. We think that the side effects and toxicity should not be a reason to state that a drug “should not be used”. It is a matter that whether the decision making on based on age, renal function and overall condition of the patient is done correctly. Obviously, gentamycin should not be used if a patient has a decreased renal function because it will lead to drug accumulation and increased toxicity.

**Conclusion**

The most important classes of aminoglycosides antibiotics are the 4, 5- and 4, 6-disubstituted 2-deoxystreptamine derivatives. Different aminoglycosides antibiotics possess different structures especially on the rings and the functional group. The differences in functional groups could be the contributing reasons to the variety of actions of different aminoglycosides antibiotics.

Two mechanisms of action involving the aminoglycosides antibiotic are by interfering with the translation by causing a misreading of the codons along the mRNA and by interfering with the translocation of tRNA from A-Site to P-site. Aminoglycosides have concentration-dependenet killing action active against the gram-negative bacilli. But, neomycin, kanamycin and gentamycin active against both gram positive and gram negative bacteria. Gentamycin is the most commonly used aminoglycosides. Aminoglycosides are not advised to be given orally because they are poorly absorbed in GIT. It is normally given via intravenous or intramuscular injection.

Aminoglycosides are very effective in treating patient with the gram negative bacteria. But, it can cause nephrotoxicity and ototoxicity and only be given when in the cases of serious gram-negative systemic infection. If it is given to the patient with renal failure, dose monitoring must be conducted to avoid serious side effects such as toxicity of aminoglycosides.

**References**


Illustrations

Illustration 1

Aminoglycoside uses

Illustration 2

Streptomycin
Illustration 3

Neomycin

Illustration 4

Gentamicin
Illustration 5

Kanamycin

Illustration 6

Mechanism of action: a) Interfering with translation by causing a misreading of the codons along the mRNA (Step I)

Aminoglycosides bind irreversibly to the 30S ribosomal subunit.
Illustration 7

Step 2

The binding of aminoacyl-tRNA to the ribosomal subunit interferes the translation process of codons on the mRNA to amino acids. On the above diagram, the codon CCG codes for the amino acid arginine. As a result of misreading, a near-match tRNA with the anticodon GAG pairs with the GCG codon. This tRNA, however, carries the amino acid leucine, not arginine. [12]

Illustration 8

Step 3

The movement of 30S ribosomal subunit continues along mRNA. Translation process continues with more amino acids were produced. On the above diagram, the codon GGA codes for the amino glycine. As a result of misreading, a near-match tRNA with the anticodon CAG pairs with the GGG codon. This tRNA, however, carries the amino acid histidine and not glycine.
b) Interfering with the translocation of tRNA from the A-Site to the P-Site (Step 1)

Illustration 9

Aminoglycoside binds irreversibly to the 30S ribosomal subunit.

Illustration 10

Step 2

Aminoglycoside prevent the transfer of the peptidy-lRNA from the A-site to the P-site, thus preventing the elongation of the polypeptide chain.
Illustration 11

Step 3

As a result, until there will be no complete polypeptide chain will be produced until the 30S ribosomal subunit reach the stop codon.

Illustration 12

Comparisons between Streptomycin, Neomycin, Kanamycin and Gentamycin

<table>
<thead>
<tr>
<th>Spectrum of Activity</th>
<th>Streptomycin</th>
<th>Neomycin</th>
<th>Kanamycin</th>
<th>Gentamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foodborne</td>
<td>Gram-negative and Gram-positive bacteria effective (e.g., tubercle bacilli)</td>
<td>Effective against Gram-negative and Gram-positive bacteria and some anaerobes</td>
<td>Effective against Gram-positive and some anaerobes</td>
<td>Effective against Gram-positive and some anaerobes</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of infections due to foodborne and waterborne pathogens (e.g., typhoid fever)</td>
<td>Treatment of upper and lower respiratory tract infections (e.g., whooping cough), meningitis or septicemia</td>
<td>Treatment of urinary tract infections; nasopharyngitis; meningitis; septicemia; endocarditis; osteomyelitis</td>
<td>Treatment of urinary tract infections (for example, by Pseudomonas aeruginosa), E. coli, Staphylococcus species</td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>A-IM injection, oral solution (oral), PO</td>
<td>A-IM injection, oral solution (oral), PO</td>
<td>A-IM injection, oral solution, PO</td>
<td>A-IM injection, oral solution, PO</td>
</tr>
<tr>
<td>Adverse effect</td>
<td>Nephrotoxicity, ototoxicity, deafness, and diarrhea</td>
<td>Nephrotoxicity, ototoxicity, deafness, and diarrhea</td>
<td>Nephrotoxicity, ototoxicity, deafness, and diarrhea</td>
<td>Nephrotoxicity, ototoxicity, deafness, and diarrhea</td>
</tr>
</tbody>
</table>

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Illustration 13

Mechanism of Resistance: a) Reduced uptake or decreased cell permeability

Illustration 14

b) Production of aminoglycoside modifying enzymes
Illustration 15

c) Alterations at the ribosomal binding sites
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