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11/21, Inuvil West
Chunnakam

TREATMENT OF LAND SNAKE BITE POISONING

by

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INTRODUCTION

1. LAND SNAKES

The majority of land snakes are non poisonous. Of the 89 species of land snakes found in Sri Lanka only 10 are poisonous. The latter are classified as follows:—

1. **The Elapids** — Fangs in front

   Cobra (**Naja naja.** — Naya=S)

   Indian Krait (**Bungarus caeruleus.** — Dhunu Karawala. Thel Karawala or Maga maruwa=S).

   Ceylon Krait (**Bungarus ceylonicus.** — Polon Karawala=S).

   Slender Coral Snake (**Calliophis melanarus**)

2. **The Vipers** Concealed fangs

   Russell's viper (**Vipera russelli.** — Tic polonga=S)

   Hump nosed viper (**Agkistrodon hypnale.** — Kunakatuwa or Polon thelissa=S). It is now placed in the genus Hypnalae and named *Hypnalae hypnalae.* Two other species in this group are *Hypnale nepa* and *Hypnalae valli.*

   Saw-scaled viper (**Echis carinatus.** — Veli polonga =S).

   Green pit viper (**Trimeresurus trigonocephalus.** — Pala polonga=S).

3. Colubridae — (1) Rat Snake - no fangs
(2) Fang at the back - Indian Snake

Bites by the last three named vipers are rarely if ever fatal to man. However symptoms such as local pain and swelling and discolouration round the bite may be seen.

The Ceylon Cat Snake (*Boiga ceylonensis* — Nidi Mapila=S) is only very mildly poisonous and cause only trivial local effects, although there is a general belief that they are highly poisonous.

2. SEA SNAKES

All sea snakes belong to the family Hydrophidae. 13 species have been recorded in Sri Lanka and are found in the coastal waters and river mouths. They sometimes swimming several miles upstream. All sea snakes are highly poisonous. One common species found in Sri Lanka is the **beaked sea snake (Enhydrina Schistosa.** — Valakkadiya=S) found chiefly in the Gulf of Mannar.

This article will be devoted to the effects of land snake bites and their treatment.

Pharmacology of Venoms

Snake venoms are secreted by modified parotid glands and serve to immobilise the prey as well as assist in its digestion. They are generally complex mixtures, consisting chiefly of:—

(a) Toxins which are chiefly low molecular weight polypeptides.

(b) Enzymes such as proteases, phospholipases and nucleotidases etc.

(c) Amines such as serotonin.

(a) Neurotoxic effects

They are very rapid in onset in the case of cobra or krait bites and consist of drowsiness, haziness of vision, ptosis and diplopia due to partial or complete ophthalmoplegia and difficulty in swallowing due to glossopharyngeal palsy. Weakness of the limbs and respiratory distress due to paralysis of the respiratory muscles may also be seen. Ptosis and ophthalmoplegia are the earliest signs of systemic poisoning in all our land snake bite poisoning except in the case of bites due to *Echis carinatus*.

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(b) **Haemorrhagic effects**

Haemorrhagic effects include bleeding from the site of the bite, ecchymoses, subconjunctival haemorrhages, bleeding from the gums, haemoptysis and gastrointestinal bleeding. An early sign of impaired coagulation is blood stained spntum detected by asking the patient to cough hard and spit. Later, blood shows no signs of clotting.

(c) **Haemolytic effects**

Haemolysis commonly follows viper bites and tests for haemolysis are positive. Urine is also dark coloured.

(d) **Cardiovascular effects**

A fall of blood pressure and shock may be seen in severe cases, E.C.G. changes such as inversion of the T. waves and S-T segment deviations may occur in severe systemic poisoning.

Prognosis

In patients with systemic poisoning treated with anti-venom, symptoms resolve rapidly, usually in a few hours to three days in the case of elapid bites although rarely symptoms may persist for 1-2 weeks. Symptoms of systemic poisoning following viper bites usually resolve within a week.

Mortality from snake bite is low. In 3 different studies of patients admitted to hospitals in this country suffering from snake bite, the mortality rates were 13.4% (Visuvaratnam et al. 1970), 11.5% (Karunaratne & Anandadas, 1973) and 8.6% (Yoganathan, 1973).

Deaths occur more rapidly after elapid bites (average 5 hours) than after viper bites (average 2-3 days). Deaths from elapid bites are mainly from respiratory failure, while in the case of viper bites the main causes are shock, haemorrhage into vital organs and renal failure.

Where local effects are concerned, swelling usually disappears in two-three weeks although in rare instances it may persist for 2-3 months. Blisters rupture spontaneously in about 2 weeks and dry up. Necrotic lesions may take several weeks or months to heal depending on the extent and the presence of bacterial infection.

Treatment

Treatment of snake bite could be divided into:—

(1) First aid treatment

(2) Treatment in hospital

(1) **First aid treatment**

First aid treatment is defined as measures taken by the victim or associates before reaching a hospital. This should not be confused with medical treatment which is given by a doctor in hospital.

First aid measures should be short, simple, practical and beneficial rather than harmful.

They consist of:—

(1) **Reassurance**

Reassurance is the most important first aid measure, as death rate from snake bite is low and the danger of snake bite is greatly exaggerated. As a result the commonest symptoms are fright and the fear of death.

(2) **Immobilisation of the bitten part**

The patient should be kept at rest and the bitten part immobilised as for a fracture. The reason for this is that the venom is absorbed rapidly from the area of the bite and distributed to the rest of the body via the lymphatics and the duperficial veins and absorption is hastened by muscular activity in the limb which is bitten. The bitten part must therefore be immobilised as quickly as possible by splinting in some way to restrict movement of the limb, which would otherwise hasten this process. Immobilisation also eases the pain. The limb should be kept in a dependent position as this serves to reduce the lymphatic flow. The patient should not be allowed to walk or run for help but should be carried.

(3) **Application of a tourniquet**

A lightly constricting ligature should be applied using a handkerchief or a piece of cloth just proximal to the bitten area tight enough to occlude the superficial veins and lympatics draining the bitten area but

without impending the arterial blood flow. This will restrict diffusion of the venom from the area of the bite and delay systemic absorption of venom, if venom has been injected, as has been shown in studies using tagged snake venom.

The tourniquet should not be applied too tight for if the arterial circulation is occluded it can precipitate or aggravate local necrosis. It must be loosened for 1 minute in every 30 minutes. The tourniquet should be taken off only when specific therapy has been instituted.

(4) Local treatment of the bitten area

The bitten surface should be washed with plain water or wiped without rubbing, to get rid of any venom that may have spilt from the fangs, and which may be absorbed later. Local application of chemicals such as potassium permanganate crystals is useless and may even aggravate the injuries sustained as a result of the bite.

(5) Administration of an analgesic

An analgesic such as paracetamol may be administered for the pain. Morphine or pethidine are contraindicated because of their respiratory depression action. Aspirin should be avoided because it interferes with haemostasis by its antiplatelet action. If the snake has been killed the people should be asked to bring the snake for identification, for if it is non-poisonous no antivenin is needed.

Value of incision and suction

There is laboratory evidence that some of the subcutaneously injected venom can be removed by incision and suction performed over the area of the bite, only if carried out within 30 minutes of the bite. If incision and suction are done later they do very little good. Such incising may also give rise to serious complications such as infection and persistent bleeding from the wound if the venom tends to interfere with haemostasis. Incision and suction are particularly dangerous where the bite involves the hands and

feet because of the risk of injury to tendons, nerves and blood vessels when performed by laymen. It may also lead to unnecessary manipulation of the part. For these reasons incision and suction are not recommended.

(2) **Treatment in hospital**

Hospitalisation is advisable for all snake bite victims especially the cases seen within 24 hours of the bite. They should be carefully observed for early evidence of systemic poisoning.

Treatment consist of:

(1) **Immediate local treatment**

The area of the bite should be cleaned with water if it has not been done before and left alone without applying any covering or dressing. Local dressings have been found to increase the incidence of secondary bacterial infection.

(2) **Institution of specific therapy where necessary**

Since snake venoms are proteins and antigenic, antibodies to the venoms (known as antivenoms or anti-venins) can be prepared and used to neutralise the venom injected as a result of the snake bite.

Anti-venom therapy is required only if signs of systemic poisoning described earlier are present. If there is no evidence of venom being injected as a result of the bite or only the immediate local effects of the venom such as swelling are seen, anti-venom therapy is unnecessary. (Local effects of injected venom do not appear to be counteracted by anti-venom). In these cases Reid (1972) recommends administration of a placebo injection such as 1ml. of vitamin B complex injection i.m. to reassure the patient and the patient carefully observed for sometime for early evidence of systemic poisoning. There is no harm in waiting for clear evidence of systemic poisoning such as ptosis,

ophthalmophgia or blood incoagulability before administration of anti-venom because clinical trials show that anti-venom therapy is effective in such cases even if given several hours after the bite. However if a krait bite is suspected it is best to give the antivenin at once because the first systemic effects may only be weakness and ptosis and even a small dose of venom (1mg) may be fatal.

Administration of anti-venom (anti-venin)

Polyvalent anti-venom serum has been produced which contain antibodies to venoms of different snakes and can neutralise these venoms when administered. The preparation available in this country is known as **Lyophilised Polyvalent Anti-Snake Venom Serum** manufactured by the Haffkine Institute, Bombay. It is prepared by hyper-immunizing horses against the venoms of the four poisonous snakes of India, namely (1) Cobra, (2) Indian Krait, (3) Russell's viper, (4) Saw scaled viper. The plasma obtained from the hyper-immunized horses is concentrated and purified and then lyophilised by drying it from the frozen state under high vacuum. It is not effective against the hump nosed viper and the green pit viper. It may be effective against the Ceylon krait bite poisoning as an antigenic similarity with the Indian krait may be expected.

The lyophilised form is stable and retains its potency for 10 years, if stored in a cool dark place even without cold storage facilities.

The contents of each vial is dissolved in 10ml sterile distilled water. The reconstituted serum is crystal clear. Froth and undissolved particles should not be drawn into the syringe.

Mode of administration of antivenom

In order to obtain maximum benefit the serum should be administered at the first sign of systemic toxicity. Administration by intravenous drip is the most effective route. Intramuscular administration is not as effective as it may take about 12 hours for 30-40% of the injected anti-venom to reach the circulation.

Tests for serum sensitivity must be carried out first as serious reactions may occur, 0.2ml is injected subcutaneously (0.02ml in the case of persons with a positive history of allergy). If a severe reaction occurs, desensitization should be attempted with graded doses. If reactions occur even with such measures, anti-venom therapy has to be abandoned.

If the sensitivity test is negative, at least 50ml. (5 ampoules) for the average case and 100ml, (10 ampoules) for the severe cases should be diluted in 2-3 times its volume of normal saline or 5% dextrose injection and given initially slowly i.v. at a rate of 15 drops per minute. If a reaction occurs the drip should be temporarily stopped and 0.5ml adrenaline 1:1000 solution given i.m. Some give 100mg hydrocortisone i.v. in addition. Usually the drip can be cautiously restarted and if reactions recur the counter measures repeated. In some cases several injections of adrenaline are needed. If no reaction is seen with initial slow administration the speed of administration is progressively increased so that the infusion is completed within about an hour.

The dosage of anti-venom for children is the same as that for adults. In patients with evidence of systemic poisoning the response to anti-venom therapy is dramatic. In neurotoxic poisoning if there is little significant improvement within an hour the dose should be repeated because polyvalent anti-venoms are usually less potent against elapid than against viper venoms.

Local effects of venom such as necrosis is not affected by i.v. anti-venom therapy. Studies with radio active material indicate that local injection of anti-venom does not confer any additional benefit.

Value of corticosteroid therapy

Although corticosteroids have been recommended for snake bite poisoning, the value of such therapy is doubtful. In animals experimentally poisoned with cytotoxic snake venoms, it has been found that corticosteroids do not affect

the survival rate. The present opinion is that corticosteroids should only be used as an adjuvant to anti-venom therapy for the treatment of reactions to anti-venom. Predinisolone 30mg orally or hydrocortisone sodium succinate 100mg i.v. should be used in such cases. Some however give hydrocortisone i.v. routinely to all patients in the belief that while it does no harm, it may do some good.

Treatment of immediate complications

(1) **Shock**

Shock is often seen after viper bites and is due to haemorrhage particularly in anaemic patients. It is best treated with blood transfusions. Metaraminol 10mg i.m. is often useful as a transient measure. Anti-venom therapy alone is effective in combatting shock not due to haemorrhage, if given in adequate dosage.

(2) **Acute renal failure**

In severe systemic poisoning, acute renal failure may occur with bites by all types of poisonous snakes, usually several days after the bite.

It is therefore important in all cases of severe snake bite poisoning, to chart the urine and the urine specific gravity daily. An early indication of impending renal failure is a low urine volume and low specific gravity. A high fluid intake during the early period following the bite, can help in preventing the onset of renal failure. About 3 litres of 5% dextrose should be given during the first 24 hours following the bite. The patient should be observed for evidence of a rising jugular venous pressure or crepitations at the lung bases, indicating overhydration and i.v. fluid therapy stopped in such instances.

If oliguria occurs, 200ml of 20% mannitol should be given intravenously. If it fails to increase the urint output the dose may be repeated and if yet there is not response, treatment as for established renal failure must be instituted, namely fluid restriction (400ml/day combined with peritoneal dialysis when indicated).

(3) **Respiratory paralysis**

If respiratory paralysis develops, tracheostomy may be required, followed by artificial ventilation. For most cases insertion of an endotracheal tube and positive pressure ventilation is sufficient.

(4) **Severe glossopharyngeal palsy**

Patients should be nursed in the prone position to prevent vomit or secretions from the throat being inhaled. Intragastric feeds or intravenous infusion may be required in such cases till the symptoms disappear in 2-3 days.

(5) **Complications due to Ayurvedic treatment**

(a) **Aspiration pneumonia** following administration of medicines through the nostrils. ("Nasna")

(b) Infection of the site of the bite due to application of herbal pastes (Pathu).

Treatment of delayed complications

(1) **Blisters**

Blisters around the site of the bite are commonly seen in poisoning due to viper or cobra bites. Blisters are best left alone and no dressing applied. They rupture spontaneously about two weeks after the bite and dry up within a week or two, provided there is no underlying necrosis. Application of dressings often result in infection resulting in greatly prolonged healing time.

(2) **Necrosis**

Local necrosis is seen usually after cobra bites and may take several days to appear. It can be extensive but is usually superficial. In rare cases it may involve muscle

and tendons. As soon as local necrosis is obvious, sloughs should be excised. The best local dressing after excision of sloughs is normal saline. Skin grafting may be needed if sloughs are excessive.

Other measures which are used if necrosis occurs are:—

(a) **Systemic antibiotic therapy** to combat any infection. If it occurs benzyl penicillin 1 million units is given i.m. twice daily till the wound has healed.

(b) **Measures for the prevention of tetanus**

In rare instances, deaths have occurred due to development of tetanus as a late complication. Therefore in the case of non-immunized patients some advocate a prophylactic dose of tetanus anti-toxin (1500 units) i.m. routinely to every patient. Others prefer to give it only if necrosis is clinically evident. If the patient has been actively immunized then toxoid should be given instead of anti-toxin.

Value of exchange blood transfusion

A limited study of exchange blood transfusion in the treatment of Russell's viper bite has shown a striking reversal of the neurotoxic effects. Correction of blood loss and haemolysis may also be achieved. Further studies are necessary to determine clearly the value of this form of therapy. It may be tried if no beneficial effects are seen in 12-18 hours after administration of anti-venom. About 6 pints of blood are necessary for an exchange transfusion (Peiris, *et al.* 1969).

References

Karunaratne, K. de S. & Anandadas, J. A., (1973) **Ceylon Medical Journal 18.** 37.

Peiris, O. A. & Nimalasuriya, A. (1969) **Postgraduate Medical Journal, 45.** 627.

Reid, H. A. (1972a) **In Manson's Tropical Diseases, 17th.** Edition. Edited by Wilcocks, C. & Manson Bahr. P.E.C. p.801, London: Baillieire, Tindal Cox.

Reid, H. A. (1972b) **Tropical Doctor, 2.** 155.

Visuvaratnam, M., Vinayagamoorthy, C. & Balakrishnan, S. (1970) **Journal of Tropical Medicine & Hygiene, 73. 9.**

Yoganathan, S. (1973) **Ceylon Medical Journal, 18.** 86.

THE NEWER AMINOGLYCOSIDE ANTIBIOTICS

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The aminoglycoside antibiotics are so called because they are composed of aminosugars connected by glycosidic linkages.

The oldest antibiotics in this group are:—

Streptomycin
Kanamycin
Neomycin & Framycetin
Paromomycin

The newer members of the group are:—

Gentamicin
Tobramycin
Amikacin
Sisomicin
Netilmicin

Spectrum of Antibacterial Activity

They are effective against Gram-negative aerobic bacilli. These include members of the family, Enterobacteriaciae such as the Esch. coli, Enterobacter, Klebsiella, Proteus Providencia and Serratia. They are also effective against the Pseudomonas.

Salmonella and Shigella are also susceptible both in vitro and in vivo but aminoglycosides are seldom used to treat Shigella or Salmonella infections because equally or more effective but less toxic antibacterial agents are available.

Gram Positive Bacteria such as Staphylococci including strains resistant to other antibiotics were originally highly sensitive to gentamicin but resistant strains have now been reported. Streptococci are usually resistant but a combination of benzylpenicillin and gentamicin is synergistic against enterococci (Strep. faecalis).

Mechanism of action

The aminoglycosides are bactericidal. They interfere with bacterial protein synthesis by binding to a particular protein site of the 30S subunit of bacterial ribosomes. This binding of the amino-glycosides to the subunit results in a misreading of the m-RNA codons. Consequently wrong aminoacids are incorporated into growing peptide chains and faulty bacterial proteins are produced.

It has also been postulated that aminoglycosides cause detachment of ribosomes fromm-RNA and cell death ensues.

Bacterial resistance

Certain bacteria produce enzymes that inactivate the aminoglycosides. Some enzymes will inactivate certain aminoglycosides but not others. The clinical implications are obvious. If an organism becomes resistant to one aminoglycoside it may still be sensitive to another aminoglycoside. For example strains of Pseudomonas resistant to gentamicin or tobramycin may be sensitive to amikacin.

Pharmacokinetics

They are very poorly absorbed from the gastrointestinal tract, usually less than 1% of a given dose. Repeated oral administration may result in accumulation in toxic concentrations in patients with impairment of renal function. Aminoglycosides when applied topically to large wounds, or burns may cause systemic toxicity in patients with impaired renal function.

They are well absorbed after i.m. administration, peak levels occurring in 30-90 minutes. Once absorbed they are well distributed throughout the body but diflusion into the CSF and eye is poor even in the presence of inflammation. Intrathecal or intra-ventricular administration may be necessary in cases of gram-negative bacterial meningitis.

Similarly, since penetration into ocular fluids is poor, periocular injection of aminoglycosides is necessary in bacterial endophthalmitis due to susceptible organisms.

In the case of neonates, intrathecal administration does not confer additional benefit probably because penetration into the CSF from the blood is better in them because of immaturity of the blood brain barrier.

They are not metabolised in the body and virtually all of the administered drug is excreted unchanged by the kidney by glomerular filtration. Urine concentrations range from 50 — 200 mcg/ml.

Adverse effects

The most important adverse effects of the group are those affecting the cochlear — vestibular apparatus and the kidneys.

1. **Ototoxicity**

It is due to destruction of the vestibular and to some extent the cochlear hair cells. Vestibular damage manifests as nystagmus, vertigo, nausea and vomiting and acute Meniere's syndrome. Cochlear damage results in tinnitus, a sensation of fullness of the ears and loss of perception of tones at high frequencies.

Ototoxicity is related to high serum levels of the drugs for periods of 10 days or more. The toxic effects are related more to the peak concentration than the traugh concentration. Prolonged peak levels above 12 ug/ml and trough levels above 3 ug/ml should be avoided. Penetration of the drug into the perilymph of the inner ear occur predominantly when such blood levels are exceeded. Back diffusion into the blood is also low with high blood levels, and is facilitated when plasma concentrations fall to low levels.

Prolonged use of aminoglycosides, high dosage and pre existing renal disease increase the incidence of ototoxicity.

The frequency of ototoxicity varies to some extent with the aminoglycoside. In large scale surveys it has been

found that the incidence is about 2% for gentamicin, 1% for tobramycin and 3% for amikacin, in patients who are treated for less than 2 weeks. Sometimes ototoxicity may manifest 10-14 days after stopping gentamicin therapy. Such instances are rare except in patients with marked impairment of renal function.

Some drugs potentiate the ototoxic effects of aminoglycosides and their use concurrently should be avoided if possible. These include ethacrynic acid and frusemide.

Local instillation of gentamicin ear drops may cause damage to the inner ear and deafness if the ear drum is perforated. Use of gentamicin ear drops is therefore not advocated (Jones R.A.K. 1978. Lancet, 1. 1161).

2. **Nephrotoxicity**

Aminoglycosides may damage the proximal tubular cells of the kidney and with moderate doses there is cloudy swelling of the cells but with high doses there is acute tubular necrosis. The renal damage is probably related to the accumulation of these antibiotics in the renal cortical tissue. It may persist for days after a single dose of the drug. The nephrotoxicity is related more to the trough levels. Renal damage is usually reversible if the drugs are discontinued at the first signs of renal damage such as a rising blood urea, serum creatinine, the presence of casts in the urine and proteinuria. Oliguria may or may not be present.

Various renal proximal tubular enzymes may be excreted in the urine during the very early stages of renal damage and the finding of lysosomal hydrolase enzymes in the urine is one of the earliest signs of nephrotoxicity and precedes the rise of serum creatinine. However most laboratories are unable to perform such tests.

These drugs should be used cautiously in patients with pre-existing renal disease and where other factors known to impair renal function such as dehydration are present.

Several drugs are capable of potentiating aminoglycoside induced nephrotoxicity. These drugs are:—

Methoxyflurane
Polymyxins
Amphotericin-B
Vancomycin
Frusemide
Etnacrynic acid

Some reports have revealed enhanced nephrotoxicity of aminoglycosides with the cephalosporins-cephalothin and cephaloridine although this was not seen in one study. However the consensus of opinion is that there is probably an increased risk of nephrotoxicity when aminoglycosides are used in combination with these two cephalosporins.

The incidence of clinically significant renal damage varies with the aminoglycoside. Mild abnormalities of renal function occur in about 8% of patients given gentamicin or tobramycin and more severe effects occur in about 2%. In controlled studies the toxicity of tobramycin has been found to be less than that of gentamicin.

Neuromuscular blockade

Aminoglycosides may rarely cause neuromuscular blockade resulting in respiratory paralysis and respiratory arrest.

Apnoea may occur

1. After rapid i.v. injection
2. Administration to patients with myasthenia gravis
3. Concomitant use of neuromuscular blocking agents

The blockade can usually be counteracted by prompt administration of neostigmine or calcium gluconate if there is no response to neostigmine.

4. **Hypersensitivity reactions**

Allergic skin rashes may very rarely follow systemic gentamicin therapy and also with local application of gentamicin cream or ointment. **Anaphylaxis** has been reported following i.v. gentamicin administration (Hall, F. J. 1977. Lancet. 2. 455).

Use in pregnancy

The safety of gentamicin during pregnancy has not been established. It is known to cross the placenta but whether this could result in ototoxicity to the fetus is not known.

Interaction of gentamicin with other drugs

The most important interaction seen in clinical practice is that between gentamicin and the anti-pseudomonal penicillins such as **carbenicillin** and **ticarcillin.** Although gentamicin shows marked synergy with the latter drugs against gram negative rods, they cause chemical inactivation of gentamicin both in vivo and in vitro, leading to loss of bactericidal activity. Therefore these drugs should not be mixed in infusion fluids or syringes but given separately. The inactivation occurring in vivo at body temperature is very slow if the drugs are given separately and therefore a synergistic effect may be obtained. However in uraemic patients the half life of gentamicin may be considerably shortened if the patient is also receiving carbenicillin or ticarcillin.

Clindamycin appears to interfere with the bactericidal activity of aminoglycosides while gentamicin has been shown to potentiate the production of pseudomembranous colitis by clindamycin. Therefore they should not be used together.

Toxic effects are enhanced when the anti-fungal drug **flucytosine** is given together with gentamicin in patients with impaired renal function. Gentamicin also enhances the nephrotoxic effects of **cephaloridine** and such as a combination is best avoided.

Causes of poor response to aminoglycoside therapy

Treatment of susceptible infections with aminoglycosides usually results in a significant response in 24-48 hours. A poor response may be due to:—

1. **Natural or acquired resistance to the aminoglycoside**

2. **Inadequate dosage**

The minimum inhibitory concentration (MIC) of aminoglycosides particularly against Pseudomonas and coliforms is high and therefore high peak levels must be attained. In some patients adequate peak concentrations may not be attained with the dosage used and the response may be poor. The peak level should be estimated in such cases and the dosage adjusted to achieve a serum concentration, 4-8 times the in vitro MIC.

3. **Inability of the drug to reach the site of infection**

This is seen for example in meningitis as diffusion into the CSF is poor.

4. **Neutropenia**

Aminoglycosides have a poor bactericidal effect in neutropenic patients particularly against Pseudomonas infections.

Clinical value

They are the most valuable drugs at present available for the treatment of serious life threatening infections caused by Gram-negative bacilli.

Aminoglycosides although potent antibiotics:

1. Are relatively expensive
2. Produce ototoxicity and nephrotoxicity
3. Their excessive use has led to the emergence of resistant strains to them particularly Pseudomonas, Klebsiella, Proteus, Providencia and Serratia.

For these reasons they must be used only when there are clear cut indications and when less expensive and less toxic drugs are not effective. It is best therefore to select one aminoglycoside for primary use preferably gentamicin or tobramycin and to keep the other aminoglycosides like amikacin in reserve for treatment of patients with infections caused by organisms resistant to gentamicin or tobramycin.

Clear cut indications for use

They are:—

1. **Gram negative septicaemia**

Gentamicin has been widely acknowledged as the drug of first choice in the treatment of life threatening septicaemia due possibly to aerobic gram negative bacilli as it is effective against most of the commonly encountered members of the group.

For initial emergency treatment of a septicaemia before the causative organism is identified it is best combined with other drugs. For example in septicaemia in cancer patients with neutropenia, gentamicin is best given in combination with **carbenicillin** or **ticarcillin.** In septicaemia associated with intra-abdominal or female genital tract sepsis both aerobic as well as anaerobic Gram-negative bacteria may be involved and gentamicin is best combined with **metronidazole** intravenous. (or clindamycin)

2. **Serious pseudomonas infections**

A combination of **carbenicillin** or **ticarcillin** and an aminoglycoside should be considered for the treatment of serious Pseudomonas infections, as the combination exerts a synergistic effect against this organism in vivo.

3. **Pneumonia due to gram-negative bacilli**

This is seen in hospitalized patients, patients on respirators and those with impaired defence mechanisms of the body; gentamicin or tobramycin is used usually in combination with **carbenicillin** or **ticarcillin** particularly if the

causative organism is Pseudomonas. Gentamicin is best combined with a cephalosporin against Klebsiella and in combination with ampicillin against Esch. coli and Proteus mirabilis.

4. **Urinary tract infections**

Although gentamicin is effective against many of the organisms causing urinary tract infections, it is not generally used for these conditions because of the availability of equally effective and safer oral drugs. It is however valuable for the treatment of infections due to Gram negative aerobic bacilli resistant to the commonly used drugs and particularly if such infections occur in an abnormal urinary tract.

The antibacterial effect is greatly enhanced in an alkaline urine and if the urine is diluted. A concentrated urine has an inhibitory effect on the antibacterial activity.

5. **Bacterial endocarditis due to Strep. faecalis or gram negative bacilli**

A combination of benzylpenicillin and gentamicin has a synergistic effect in *Strep. faecalis* endocarditis and is now the combination of first choice in this condition.

A gentamicin/carbenicillin combination is effective in Ps.aeruginosa endocarditis and also in some cases of *Serratia marcescens* endocarditis.

6. **Severe staphylococcal infection**

Gentamicin is a valuable drug for use alone or in combination with other drugs for infections due to staphylococci resistant to the penicillinase resistant penicillins like cloxacillin or flucloxacillin. Aminiglycosides such as gentamicin shows in vitro synergy against *Staphylococcus aureus* when used in combination with a penicillinase resistant penicillin or cephalosporin. Such a synergistic drug combination would be useful in Staphylococcal endocarditis not responding to penicillinase resistant penicillins or cephalosporins, despite sensitivity of the strains in vitro to these drugs.

7. Topical uses of gentamicin

Gentamicin is generally not recommended for topical use because of the development of resistant strains after such use, causing serious problems. The special circumstances in which gentamicin is indicated for topical use are:—

(a) Severe infected burns

The use of local application of gentamicin in burns should be restricted as far as possible because it encourages emergence of gentamicin resistant bacilli. Its use should be limited to severe infected burns due to Pseudomonas that are life threatening and where 20% or more of the total body surface is involved. Parenteral therapy is also indicated if there is associated septicaemia.

(b) Eye infections

Corneal ulcers and bacterial endophthalmitis are often due to Gram negative bacilli such as *Pseudomonas* and respond to local application or subconjunctival injection of gentamicin.

8. Neonatal meningitis

For initial chemotherapy before the causative organism is identified, the treatment of choice is **ampicillin combined with gentamicin.** If the causative organism is a Gram negative bacillus such as *Each. coli, Klebsiella spp.* or Pseudomonas, gentamicin is effective given parenterally **alone.**

The role of intrathecal gentamicin in conjunction with parenteral treatment for meningitis is controversial and there is doubt whether any clinical benefit accrues from intrathecal gentamicin (Mc Cracken G. M. Jr. & Mize, S. G. (1976) **J. Paediatrics. 89.** 66). Problem patients not responding or not likely to respond to parenteral therapy alone, should be given the drug intraventricularly as well.

9. **Biliary tract infections**

Gentamicin in combination with ampicillin or one of the cephalosporins is useful in treating **acute cholangitis.** In seriously ill patients particularly the elderly, there is the additional possibility of a Gram-negative anaerobic bacterial infection and therefore metronidazole or clindamycin may be given in addition.

Gentamicin and/or a Cephalosporin has been successfully used as a single dose just before surgery to prevent post operative sepsis after elective cholecystectomy or performed during the first week after an attack of acute cholecystitis. (Cunha, B. A., Pyrick, L. J. & Quintilliani, B. (1978) Prophylactic antibiotics in cholecystectomy **Lancet** 1. 207).

Preparations of newer aminiglycosides

1. **Gentamicin**

1. **Gentamicin sulphate injection**

A sterile aqueous solution containing gentamicin sulphase 40mg per ml in 2ml vials for i.m. and i.v. use. The solution is stable at room temperature and does not require refrigeration.

2. **Gentamicin paediatric injection**

A sterile aqueous solution containing gentamicin sulphate 10mg per ml in 2ml vials.

3. **Gentamicin intrathecal injection**

Available as proprietary preparations of different strengths.

(a) **"Genticin intrathecal injection"** (Nicholas). Aqueous solution containing 1mg/ml

(b) **"Garamycin intrathecal"** (Schering). Aqueous solution containing 4mg/2ml

4. **Gentamicin topical applications**

(a) **Gentamicin Eye/Ear drops**
Contains 0.3% gentamicin sulphate

(b) **Gentamicin Cream & Ointment**
Contains 0.3% gentamicin sulphate

Parenteral dosage

All aminoglycosides have a low therapeutic index, the therapeutic dose being quite close to the toxic dose. There is also a considerable variation among individuals both in the peak as well as trough serum levels of the drug produced by a given dose and in the half life of the drug.

Successful therapy depends on achieving adequate peak levels while high trough levels lead to toxicity. Where facilities are available it is best to measure the peak and trough levels every few days to ensure that the patient is neither being overdosed or underdosed.

The acceptable peak and trough levels for the different aminoglycosides are shown in the table below and the dose should be adjusted accordingly.

Aminoglycosides	Desirable serum levels	
	Peak (ug/ml)	Trough (ug/ml)
Gentamicin & Tobramycin	6 — 10	< 2.0
Amikacin	20 — 30	< 8.0
Sisomicin	4 — 10	< 2.0
Netilmicin	10 — 20	< 5.0

The peak serum level is estimated by taking a blood sample one hour after an intramuscular dose and 15 minutes after an i.v. dose. To estimate the trough levels, a blood sample must be taken just before the next dose.

Where facilities are not available to estimate the blood levels the dosage is estimated on the basis of body weight.

The adult dose is 3-5mg/kg body weight per day given usually by intramuscular injection in equally divided doses 8 hourly. The higher dosage is necessary for severe infections. For patients weighing over 60kg the average dose is 80mg every 8 hours.

The intravenous route is essential for patients in shock and also for those who have a bleeding tendency. Each dose is added to 50-200ml of 5% dextrose or 0.9% sodium chloride injection and administered over a period of 30 minutes. It is given in a smaller volume of diluent over a period of 1-2 hours in the case of infants. (U.S. Pharmacopoeia dispensing information 1981. p 310).

Intrathecal administration

Penetration of gentamicin into the CSF after intramuscular administration is not sufficient to produce therapeutic concentrations in the CNS, and so intrathecal or intraventricular administration is also used in the treatment of meningitis.

The preparation available for parenteral administration contains preservatives and is not suitable for intrathecal use. **Adult dose** is 2-4mg daily.

After haemodialysis

Aminoglycosides are removed only in small amounts by peritoneal dialysis but in large quantities during haemodialysis. Therefore patients requiring haemodialysis and gentamicin therapy should begin supplemental doses of gentamicin 1-1.7mg/kg of body weight, depending on the severity of infection, after each haemodialysis.

Patients with impaired renal function

Whenever possible the serum levels of gentamicin should be determined to help in modifying the dosage to avoid toxic effects. Modification is chiefly in the frequency of administration which will depend on the degree of impairment of renal function. When renal function is impaired the peak and trough levels after a given dose are raised and the halflife prolonged.

In order to saturate the tissues and fluids with adequate concentrations of the antibiotic, the initial dose is the same as that for patients with normal renal function irrespective of the degree of renal impairment, but the interval between raised and the half life prolonged.

There are several methods of calculating the interval between doses if serum levels cannot be estimated. A convenient one is based on measurement of creatinine clearance and is as follows:—

Creatinine clearance	Interval between doses
30—70 ml/min	12 hours
10—30 ml/min	24 hours
5—10 ml/min	48 hours

Other methods are based on estimation of the serum creatinine concentration or use of nomograms but calculations of dosage based on all these methods are only approximations.

Children's dosage

Children need relatively higher doses of gentamicin than adults to achieve similar serum levels. The serum gentamicin half life is prolonged during the first week of life. The recommended doses for children are:—

Newborn & premature infants — 5mg/kg/day in two divided doses at 12 hour intervals.

Children under 5 yrs. of age — 7.5mg/kg/day in three divided doses at 8 hour intervals.

Children 5 — 10 years of age — 6mg/kg/day in three divided doses at 8 hour intervals.

Intrathecal dose:—

Infants up to 3 months — dose not established
3 months of age and over — 1-2mg once a day.

Preparations of Aminoglycosides available in Sri Lanka

Trade Name	Manufacturer	Cost (Retail) in Rupees
Lyramycin	Lyka Labs. India.	Rs. 24.00
Garamycin	Schering	Rs. 35.42
Gentasporin	Pharmaceutical Co. of India	Rs. 16.60
Ensamycin (Sisomicin)	Schering	50mg — Rs. 48.50 75mg — Rs. 59.30

TOBRAMYCIN "NEBCIN" (LILLY)

Tobramycin has a spectrum of antimicrobial activity similar to gentamicin with however few important exceptions. It is 2-4 times more active by weight than gentamicin against some strains of *Pseudomonas aeruginosa.* It is also less active against *Serratia marcescens* and enterococci such as *Strep. faecalis*.

In the case of *Pseudomonas aeruginosa* there is cross resistance between gentamicin and tobramycin which however is not complete. Strains with low level of gentamicin resistance, are susceptible to tobramycin.

Staph.aureus including penicillin resistant strains are sensitive to tobramycin but *Strep. peumoniae Strept. pyogenos* and *viridans* have a low degree of sensitivity or are completely resistant to it.

Tobramycin when combined with carbenicillin is more effective than tobramycin alone in severe *Pseudomonas aeruginosa* infections.

Resistance

There is almost complete cross resistance between tobramycin and gentamicin.

Adverse effects

Tobramycin like other aminoglycosides cause both ototoxicity and nephrotoxicity. Studies in animals suggest that it causes less cochlear and vestibular damage and less renal tubular damage than gentamicin but this has not been conclusively established in human subjects although some preliminary data supports this view.

Clinical value

Indications for the use of tobramycin are similar to those for gentamicin. However tobramycin is preferable for the treatment of Pseudomonas infections because of its superior activity against this organism. In confirmed severe Ps aeruginosa infections it should usually be used in combination with carbenicillin or ticarcillin.

Gentamicin is preferred for *Serratia marcescens* infections as it is about 4 times more active than tobramycin.

It is of no value in the treatment of gentamicin resistant enteric Gram-negative infections other than Pseudomonas infections.

AMIKACIN "AMIKIN" (BRISTOL)

It is the first semisynthetic aminoglycoside produced and is a derivative of kanamycin A.

It has a broad spectrum of activity similar to gentamicin. It is resistant to most of the bacterial enzymes that inactivate gentamicin, tobramycin and kanamycin and therefore it is active against many tobramycin and gentamicin resistant strains of Enterobacteriacae, penicillinase producing staphylococci are uniformly insensitive.

It is similar to kanamycin in its pharmacokinetic properties and dosage. Like the other aminoglycosides both ototoxic and nephrotoxic effects are seen with amikacin.

Clinical value

It is best reserved for the treatment of serious infections due to Gram negative bacilli resistant to gentamicin. It is the aminoglycoside of choice for the initial treatment of severe infections presumably due to Gram-negative organisms in hospitals or units where gentamicin resistant strains are known to occur or in patients with cancer and neutropenia. In these circumstances it is best used in combination with carbenicillin.

SISOMICIN "ENSAMYCIN" (SCHERING)

Its spectrum of antimicrobial activity is very similar to gentamicin. Some have reported that it is slightly more active than gentamicin against some Gram negative bacilli particularly Klebsiella and indole positive Proteus. It is not as active as tobramycin against *Pseudomonas aeruginosa.* Its pharmacokinetics and methods of administration are similar to those of gentamicin, and the toxicity of these two drugs is also probably about the same.

There is almost complete cross-resistance between sisomicin and gentamicin.

Clinical value

It has the same indications and uses as gentamicin and does not offer any advantage over gentamicin. It is also more expensive.

NETILMICIN "NETROMYCIN" (SCHERING)

It is a semisynthetic derivative of sisomicin and also has a spectrum of antibacterial activity similar to that of gentamicin. But most strains of *Pseudomonas aeruginosa* are approximately two fold less sensitive than to gentamicin. There is synergy between netilmicin and carbenicillin against many strains of *Pseudomonas aeruginosa.*

Unlike sisomicin it is active against a proportion of gentamicin resistant Gram-negative bacilli. Gentamicin resistant strains of *Each. cli, Proteus mirabilis,* Enteroc bacter, Klebsiella and Serratia spp are **usually** sensitive to netilmicin but gentamicin-resistant strains of *Esch. coli* and Serratia resistant to netilmicin have also been isolated. Indole positive Proteus and Acinobacter sp. resistant to gentamicin are **usually resistant** to netilmicin.

Adverse effects

Adverse effects are similar to those of gentamicin. Experimental work on animals indicate a lower cochlear toxicity when compared to gentamicin but clinical use has been limited to confirm this.

Clinical value

Netilmicin is a useful alternative to amikacin in the treatment of infections due to Gram-negative bacilli resistant to gentamicin but sensitive to netilmicin.

It has been shown that in *Esch. coli* induced meningitis in animals that netilmicin achieved better in vivo bactericidal activity than gentamicin in the CSF. For this reason and its possible lesser otoxicity it has been suggested that netilmicin may be superior to gentamicin in the treatment of meningitis due to Gram-negative bacilli.

NEW DRUGS

KETOTIFEN "Zaditen" (Wander)

Ketotifen is a new chemical compound — a tricyclic benzocyclo-heptathiophene derivative chemically related to the anti migraine drug pizotifen.

Pharmacological actions

In experimental studies in animals and man it has been shown to have:—

(a) Potent long acting antihistaminic properties and also marked anti-anaphylactic properties.

(b) A protective effect against allergen and histamine induced bronchospasm.

Mechanism of action

Its action resembles that of sodium cromoglycate in that it stabilises the mast cell membrane and blocks the release of chemical mediators such as histamine and SRS-A following an antigen-antibody reaction — mediators which are responsible for initiating the asthmatic attack.

Pharmacokinetic effect

Unlike sodium cromoglycate it is effective when given orally and is absorbed within one hour. Its effects lasts up to 12 hours.

Adverse effects

It produces drowsiness in about 10 — 15% of patients initially, which generally passes off with continued usage in a short time. Sometimes drowsiness may be so marked as to necessitate withdrawal of the drug. Other side effects include dry mouth, headache and dizziness.

Precautions and warnings

Patients should be advised to take care when driving cars or operating machinery because of the drowsiness produced. The effects of hypnotics and alcohol, are potentiated.

Clinical value

It is useful in **preventing attacks** of allergic asthma. It is as effective as sodium cromoglycate. Unlike sodium cromoglycate it takes several weeks to produce its full effects. Maximum efficacy os obtained in 6-12 weeks and this maximum effect is subsequently maintained.

In a cross-over study comparing the effects of sodium cromoglycate 20mg four times daily with ketotifen 1mg twice daily for 3 months in 60 patients ketotofen was effective in 65% and cromoglycate in 53%. The difference was however not statistically significant.

Because of its slow onset of action if it is devided to change from sodium cromoglycate to ketotifen the treatment should overlap over a period of two weeks.

Ketotifen has also been found to have an important steroid sparing effect in patients on maintenance corticosteroid therapy.

Preparations and dosage

1. **Ketotifen tablets**

   Each tablet contains 1mg ketotifen.

Adult dose: 1mg (1tab.) twice daily. Some require doses of 2mg twice daily.

Children's doses:

12-22kg	—	0.5mg (½ tab) twice daily
22-32kg	—	0.5mg (½ tab) thrice daily
Over 32kg	—	1.0mg. (1 tab) twice daily

2. **Ketotifen Syrup**

   Each 1ml contains 0.2mg ketotifen

Children's doses:

14-18kg	—	2ml (0.4mg) twice daily
19-25kg	—	3ml (0.6mg) twice daily
26-35kg	—	4ml (0.8mg) twice daily
≧35kg	—	5ml (1mg) twice daily

Cost

The approximate cost of a day's use is as follows:

	Cost of a daily dose
Ketotifen Tablets (Zaditen)	2 Tablets — Rs. 8.30
Sodium Cromoglycate (Intal)	4 Capsules — Rs. 21.40

References

1. Craps, L., Greenwood, C., Radiovic, R. (1978) Clin. Alerg. 8. 373

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