Clinical assessment and treatment of neurotoxicity

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Overview

Neurotoxicity is the major clinical consequence of all venomous snakebites in Papua New Guinea and a major contributor to fatal outcomes.

Mechanism of neurotoxicity & implications for envenomed patients

Neurotoxins can either be presynaptic or postsynaptic. Some snake venoms contain both presynaptic and postsynaptic neurotoxins. Presynaptic neurotoxins are difficult to reverse, whereas postsynaptic neurotoxicity can be reversed with anticholinesterase drugs such as neostigmine.

The neurotoxins interfere with transmission of nerve impulses from nerve endings to muscles. This occurs at the neuromuscular junction (NMJ). The presynaptic neurotoxins probably act by interfering with the release of acetylcholine (ACh), while the postsynaptic neurotoxins interfere with the action of acetylcholine, as has been explained elsewhere in this Handbook.

Neuromuscular junction (NMJ) and neurotransmission

Acetylcholine is the neurotransmitter at the NMJ which allows normal muscle activity to occur (see **FIGURE 1** – Neuromuscular junction).

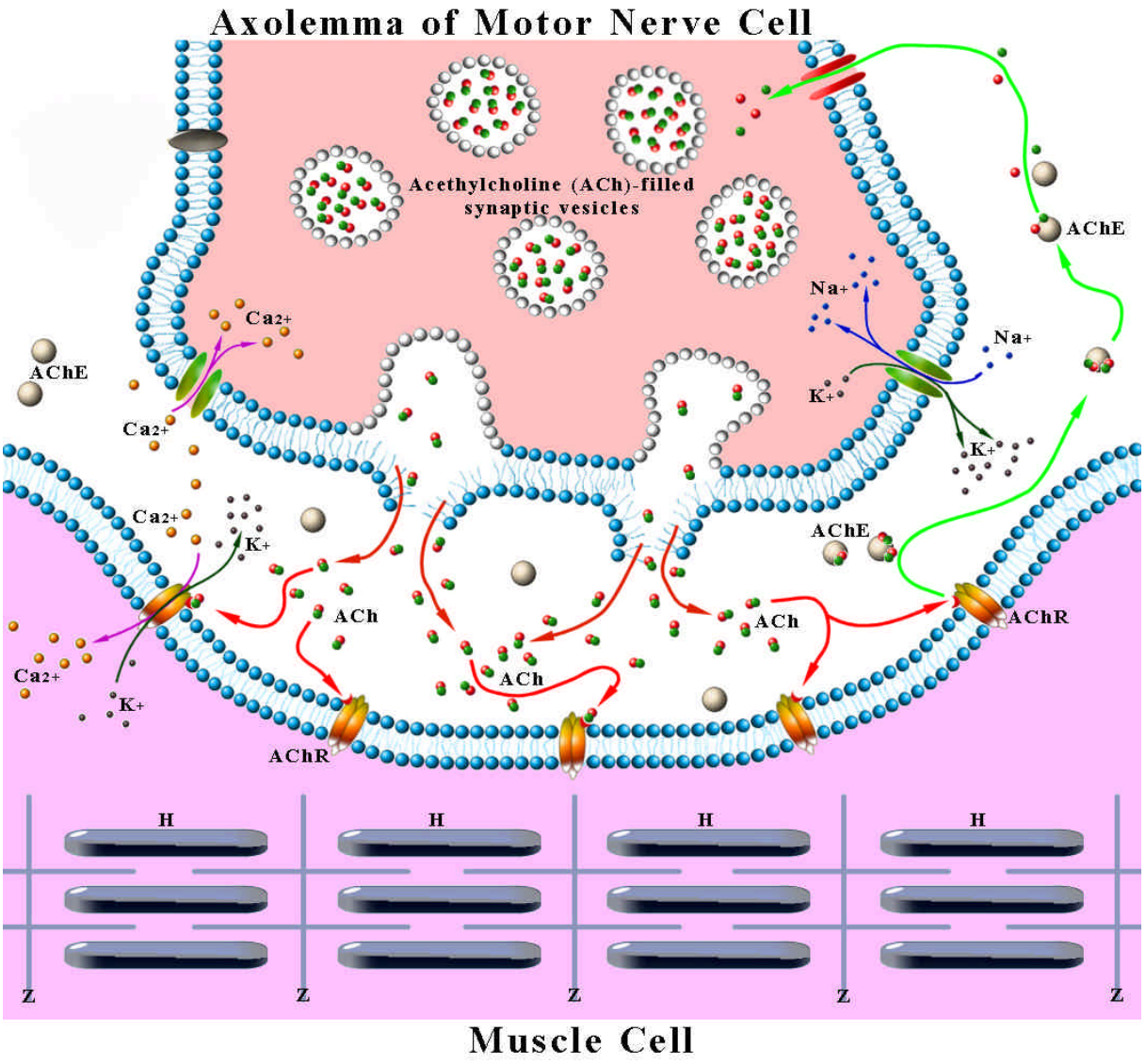
The nerve impulse arriving at the end of the motor neuron increases the permeability of the phospholipid membrane to calcium. This causes an increase in exocytosis of acetylcholine vesicles in the synaptic cleft. Acetylcholine diffuses across the synaptic cleft to bind with the acetylcholine receptors on the muscle membrane. Binding of acetylcholine to these receptors opens up the sodium-potassium pump in the muscle membrane and allows sodium to enter the muscle cell membrane. The influx of sodium into the cell produces a decrease in potential outside the muscle membrane and an increase in potential on the inside. As a result, an electrical impulse known as depolarisation potential is produced. The decrease in the potential outside also depolarises adjacent muscle membranes to their firing levels.

Postsynaptic neurotoxins competitively bind to acetylcholine receptors on ion channels in the phospholipid membrane of motor muscle cells, preventing acetylcholine from binding. This prevents depolarisation and the muscle remains paralysed. Anticholinesterases can be used to treat postsynaptic neurotoxicity because they inhibit neurotransmitter recycling and enable acetylcholine to remain in the synaptic cleft longer, increasing neurotransmitter binding to unblocked receptors, and producing depolarisation.

Presynaptic neurotoxicity is more difficult to treat because the toxins bind to transmembrane proteins on the motor neurons and not only inhibit acetylcholine release by blocking exocytosis of the synaptic vesicles, but also cause extensive physical damage to the nerve ending itself, perhaps through uncontrolled calcium influx into the neuronal cytoplasm, as has been detailed in Chapter 3. Other presynaptic neurotoxins inhibit outward potassium ion (K^+) transport, which in turn inhibits the actual recycling of the synaptic vesicles.

Impairment of neurotransmission by snake venom toxins predominates in the skeletal musculature rather than in smooth or cardiac muscle. There is evidence that does suggest, however, that some snake venom toxins may also exert effects on ion transport in the myocardium which can lead to arrhythmias and other myocardial conduction problems. Vasoactive toxins that affect endothelial cells in blood vessel walls may also have a role in hypotensive syndromes seen after some snakebites.

FIGURE 1: Neuromuscular junction showing the processes of synaptic vesicle exocytosis, acetylcholine (ACh) binding to receptors on the motor muscle, and dissociation of acetylcholine by acetylcholinesterase (AChE), followed by re-uptake of acetate and choline by the motor neuron. These processes provide many potential physiological target sites for snake venom neurotoxins; presynaptic neurotoxins affect the motor nerve ending, while postsynaptic neurotoxins affect the ability of acetylcholine to bind to the motor muscle receptors (nAChR).



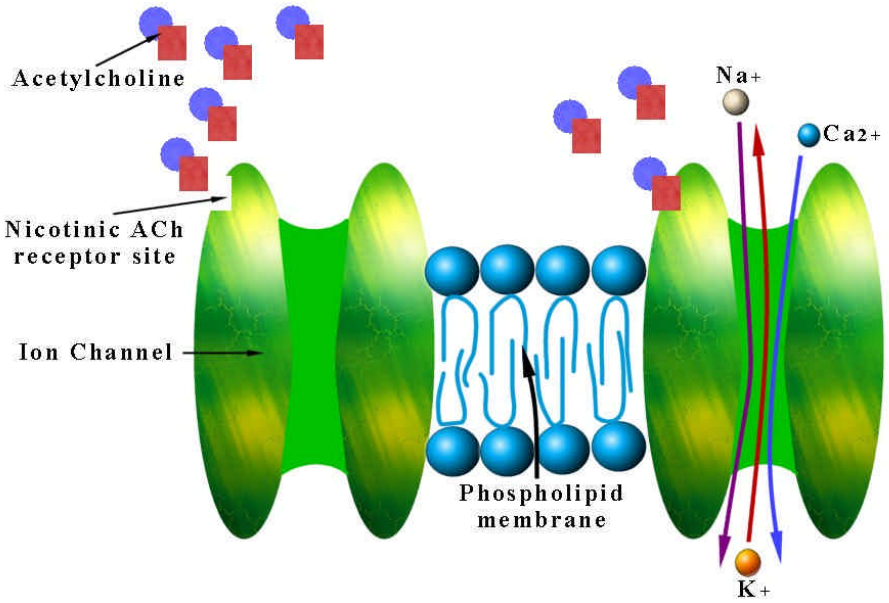


FIGURE 2: Schematic of motor muscle ion channel containing the nicotinic acetylcholine receptor (nAChR); when acetylcholine (AChR) binds to the nAChR, the ion channel is opened, allowing ions such as sodium (Na^+) and calcium (Ca^{2+}) into the cell, while potassium (K^+) is able to leave the cell and enter the extracellular space.

Assessment and Recognition of Neurotoxicity

Bites are relatively painless (with the exception of mulga snakes, and possibly the Papuan blacksnake) and may be unnoticed. Paired fang marks are usually evident, but sometimes only scratches or single puncture wounds are found. Papua New Guinean snakes do not cause extensive damage to local tissues. There may be mild swelling and slight bleeding from the bite site.

Symptoms and signs of envenomation

Not all possible symptoms or signs occur in a particular case; in some cases, one symptom or sign may predominate, while in most cases there is a mixture (see **TABLE 1**).

The earliest symptoms and signs of neurotoxicity typically involve the cranial nerves affecting the ability to control both the major and minor facial muscles. Ptosis is generally the first clinical indication of neurotoxicity and involves paralysis of the muscles responsible for opening the eyelids. Relatives and friends of a snakebite victim, and even health care workers, may often interpret ptosis as 'tiredness' or 'sleepiness'.

In a patient with a history of suspected snakebite, early ptosis is an important early indication for the administration of appropriate antivenom and should not be ignored.

Additional symptoms of neurotoxicity may include blurred vision, double vision (diplopia), slurred speech (dysarthria), difficulty in swallowing (dysphagia) and shortness of breath or difficulty breathing (dyspnoea).

On examination, the following are important clinical signs of neurotoxicity: inability to open the eyes (ptosis), fixed gaze and inability to move eyeballs (ophthalmoplegia), dysphonia, dysphagia, dysarthria, impaired ability to protrude tongue, dyspnoea, tachypnoea, limb weakness (reduced hand grip is a sign), loss of deep tendon reflexes, abdominal breathing and, in severe cases, cyanosis caused by insufficient oxygenation of the blood.

TABLE 1: Course of progressive onset of major systemic symptoms and signs of untreated envenomation. In cases of massive envenomation, or bites in children, a critical illness may develop in minutes rather than in hours.

LESS THAN 1 HOUR AFTER THE BITE

- Headache
- Nausea, vomiting, abdominal pain
- Transient hypotension associated with confusion or loss of consciousness
- Coagulopathy (20WBCT or laboratory testing)
- Regional lymphadenitis

1 TO 3 HOURS LATER

- Paresis/paralysis of cranial nerves – ptosis, double vision, external ophthalmoplegia, dysarthria, dysphonia, dysphagia, facial weakness
- Haemorrhage from mucosal surfaces and needle punctures
- Tachycardia, hypotension, tachypnoea, shallow respirations

MORE THAN 3 HOURS LATER

- Paresis/paralysis of truncal and limb muscles
- Paresis/paralysis of respiratory muscles and respiratory failure
- Rhabdomyolysis
- Dark urine (due to either myoglobinuria or haemoglobinuria)
- Renal failure
- Coma; possibly due to hypoxaemia and shock. Shock may result from intracranial haemorrhage or coagulopathy

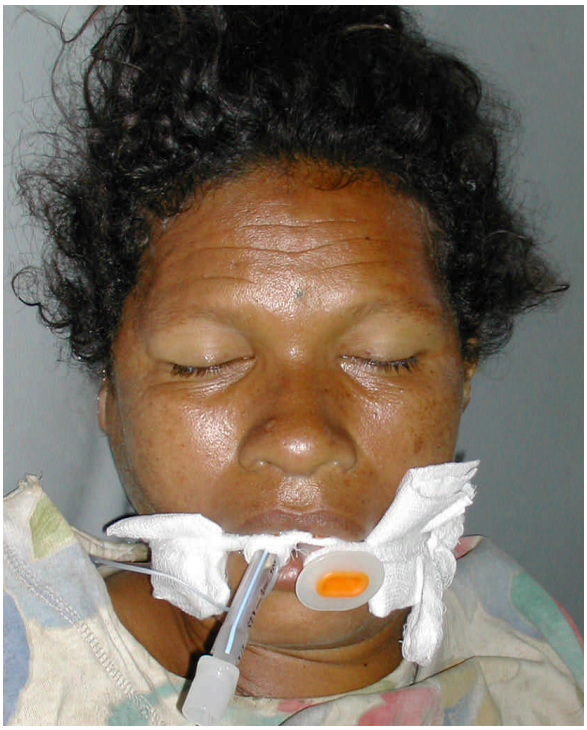


FIGURE 3: Ptosis in a patient with suspected Papuan taipan (*Oxyuranus scutellatus canni*) envenomation.

Note that despite the brow furrowing caused by the patient as she attempts to open her eyes, she is completely unable to do so.

Ptosis is a very important early sign of developing systemic envenomation and should be assessed with care; a common error is to mistakenly assume that a person with ptosis is tired or sleepy.

The person should be asked to attempt to open their eyes as wide as possible, and if unable to do so then antivenom should be given without delay, especially if the 20WBCT was positive.

Many patients with ptosis also have a varying degree of ophthalmoplegia (the paralysis of the muscles which allow the eyes to move in vertical, horizontal or diagonal planes), and you can assess this sign by asking the patient to use their eyes to follow finger movements through the sphere of vision while they keep their heads facing forward.

General Treatment Strategy

Before discussing specific treatment strategies for dealing with issues related to neurotoxicity such as respiratory support and airway protection, a general overview of some other patient management considerations is helpful:

1. **Allay anxiety and fear**
   - Reassurance.
   - Sedation – this can be achieved with use of diazepam i.v, or via an orogastric tube, but only in the intubated patient, since this may remove what respiratory drive they have left.
2. **Analgesics and antipyretics**
   - Paracetamol suppositories or crushed tablets via orogastric tube.
   - Aspirin, particularly, but also other non-steroidal anti-inflammatory analgesics, should be avoided in the case of snakebite where coagulopathy may occur, or is already present.
3. **Nutrition**
   - Insert an orogastric or nasogastric tube for feeds and medication (ideally inserted at the time of intubation), but take great care not to cause mucosal damage if there is concurrent coagulopathy.
   - Regular 3-4 hourly blood glucose checks and giving glucose-containing iv fluids when needed.
4. **Bowel and bladder care**
   - Prophylaxis against stress ulcers – cimetidine i.v. or via enteral feeding tube.
   - Insert an indwelling urinary catheter for monitoring of renal functions as well as for checking for blood, blood pigments and myoglobin.
5. **General care of an unconscious patient**
   - Hourly monitoring of vitals – pulse, blood pressure, temperature, respiratory pattern and rate, level of consciousness, pulse oximetry and urine output.
   - Hourly snakebite observations.
   - Regular gentle suctioning of secretions in the mouth and the oropharynx, and of the endotracheal tube if the patient is intubated (don't pass the catheter beyond the end of the tube).
   - Care of pressure areas by regular changing of position and massaging (gently) of pressure points; application of soft padding over these areas.
   - Limb and chest physiotherapy for those who are heavily envenomed.
6. **Oxygen therapy**
   - Supplementary oxygen should be given to every patient with respiratory failure, pulmonary aspiration or shock.
7. **Antibiotic cover**
   - This is not required unless the patient has clear skin infection or pneumonia; the use to "prevent" infection will simply select more resistant organisms to colonise the patient's wounds. However, local wound care, after antivenom has been given, is required.

8. Intravenous fluids

- These are given for shock, to replace fluid losses and for maintenance requirements.

9. Laboratory investigations

- FBE, UEC's, fibrin degradation products and clotting times.
- Blood grouping and cross-matching (unless there is clearly no coagulopathy).
- Chest x-ray if there are signs of chest infection, or after intubation of the trachea.
- Arterial blood gas analysis – in those centres with this facility; it is vital, as it not only assists in patient management, but also helps save the cost of oxygen.

Management of patients with respiratory difficulties

Airway maintenance

- Pooling of secretions (saliva), difficulty in swallowing, slurring of speech and hoarseness of voice are early signs that the airway is compromised. Therefore, it is important that suction apparatus and oxygen delivery equipment are readily available at the bedside.
- Insertion of Guedel airway may not be tolerated at this stage, unless the gag reflex has been abolished.
- Intubation of the trachea is indicated when there is marked pooling of saliva, the gag reflex is disappearing, when peripheral oxygen saturations are falling, below 90% despite oxygen, or when the patient presents with cyanosis or in respiratory arrest. They are likely to allow fairly easy laryngoscopy and intubation of the trachea.
- The use of diazepam to facilitate intubation should be used with caution, since it does little to improve intubating conditions (i.e.: make it easier for you to perform), and has a slow onset of action, but may completely remove the patient's respiratory drive before you have secured the airway. Morphine is a better drug for this, or better still, use the 2 drugs together and be prepared to manually ventilate the patient for a while once intubated. The use of suxamethonium, as well, will produce the best conditions for intubation, if you are trained in its use.
- **REMEMBER**: If you are not confident to intubate, then **do not sedate** the patient and **do not try to intubate.**
- Keep the endotracheal tube sterile at all times; otherwise you risk introducing bacteria into the lungs and causing pneumonia or tracheitis.
- Do not forcefully perform laryngoscopy or intubation. This causes pain for the patient. It also causes mucosal injury and the consequent bleeding, if coagulopathy is present, will further compromise the airway and respiration. The stimulation may also cause bronchospasm, laryngospasm, severe bradycardia (all via vagal nerve stimulation) or ventricular arrhythmias, which can each kill the patient quite quickly.
- When you intubate, someone should someone should be providing cricoid pressure, to prevent vomiting, and should monitor the pulse continuously throughout the procedure.
- If the patient resists laryngoscopy, then he or she still has the ability to maintain their own airway, for now.
- If you are unable to intubate, use the Guedel airway and a non-rebreathing, or a Hudson, mask with supplementary oxygen.
- If you have managed to intubate the patient, you must always give supplementary oxygen, since the patient will almost always need it.

- ETT insertion should be followed by very gentle orogastric or nasogastric tube insertion to empty the stomach, thus making ventilation easier and reducing the risk of reflux of gastric contents.

Assisted ventilation strategies in rural health centres

- Guedel/nasal airway with Ambu-bag and mask ventilation may be appropriate, but be aware that this can inflate the stomach with air if not done very carefully, and hence increase the risk of reflux of gastric contents, or vomiting, and pulmonary aspiration.
- Perform laryngoscopy and intubation (if you are appropriately trained), then assist ventilation with an Ambu-bag, as discussed above.
- Do not leave the intubated patient breathing through the Ambu-bag with very low flows of oxygen (less than 4 litres/minute), since their minute volume (respiratory rate times the volume of each breath) may be higher than this and they will essentially be suffocating. If you have a limited oxygen supply, it is better to use a T-piece, or to administer oxygen via a fine suction catheter that has been placed inside the endotracheal tube (ETT) with its tip not beyond the end of the ETT.
- If you are assisting the patient's ventilation, or are fully manually ventilating them with the Ambu-bag, you will need enough oxygen flow to refill the bag after each time you have squeezed it.
- Do not leave an intubated patient with relatives or untrained staff ventilating, or assist-ventilating, a patient for long periods without frequently checking that they are performing it correctly, that the ETT is still in the correct position, and that the patient's vital signs are stable and okay.
- Oxygen must be administered during assisted ventilation.
- Transport of the patient to the nearest hospital with facilities to provide ventilation must be a high priority.

Assisted ventilation strategies in urban hospitals

- Intubate and assist ventilation with Ambu-bag and mask, or a T-piece breathing circuit.
- Attach to a mechanical ventilator. The mode of ventilation depends on the respiratory drive/function of the patient. Generally two common modes are used:
  - ? Synchronized intermittent mandatory ventilation (SIMV)
  - ? Controlled mechanical ventilation (CMV)
- Sometimes patients who have normal respiratory drive, but have pulmonary oedema or pulmonary aspiration, are ventilated in the continuous positive airway pressure (CPAP) mode.

Complications of various interventions

A number of different complications can arise during efforts to maintain ventilation, depending on the particular technique that is being employed:

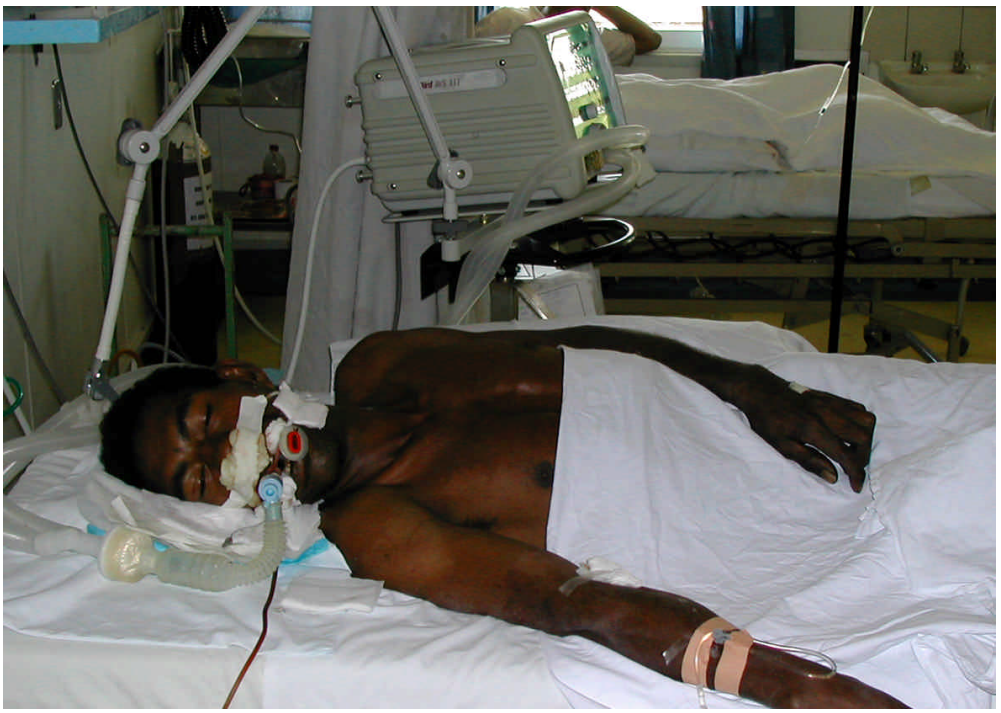
1. Guedel/nasal airway with bag and mask ventilation

- Increased risk of regurgitation and aspiration.
- Trauma to mucosal surfaces of the oropharynx and nasopharynx.
- Damage to teeth by forceful insertion of a Guedel airway.

2. Bag and mask ventilation via endotracheal tube

- Trauma to soft tissues of the mouth, oropharynx and trachea and to teeth. These are complications that often occur during laryngoscopy and intubation. Therefore care must be taken during this procedure. These complications are usually a result of inexperience and anxiety.
- Spontaneously breathing patients can rebreathe their own expired gases if inappropriately managed. Increased levels of CO_2 initially cause hypotension due to vasodilation, then later hypertension, tachycardia and CO_2 narcosis. The CO_2 narcosis can be mistaken for deepening of neurotoxicity and therefore not treated. The patient will eventually develop a coma.
- Breathing dry gases, since the normal humidifying system (nose) is bypassed. As a result there may be crust formation in the airways which can cause blockages.
- Over-inflation of the lungs may increase the risk of ruptures of the alveoli and bullae formation, causing pneumothorax.
- Under-inflation of lungs can precipitate collapse of the alveoli.

FIGURE 4: Patient with presumed Papuan taipan (*Oxyuranus scutellatus canni*) envenomation being maintained on a ventilator due to a loss of respiratory effort.



3. Assisted ventilation with mechanical ventilators

- Increased risk of transmission of infection during suctioning and the use of a breathing circuit.
- Breathing of dry gases.
- Trauma to tracheal mucosa from over inflation of endotracheal tube cuff and prolonged intubation may result in tracheal mucosal ischaemia and finally fibrosis and stenosis.
- Unequal distribution of gases and blood flow to the lung tissues (ventilation-perfusion mismatch). The alveoli on the top (i.e.: proximal in relation to gravity) are better oxygenated than those distally, which in turn are better perfused. Normally this mismatch is not so significant, but in ventilated patients this difference is increased.
- Increased risk of rupture or collapse of alveoli with over inflation or under inflation respectively.
- Increased intrathoracic pressure exerting external pressure on the major vessels such as the inferior and superior vena cava, thereby reducing venous return to the heart and eventually reduced cardiac output.

Reversal of neurotoxicity with antivenom

In Papua New Guinea the selection of antivenom has typically been a decision that is made on the basis of one or more of the following:

1. An identification of the snake responsible by the patient or by those who were with the patient at the time of the bite.
2. A good description of the snake by the patient or those who were with the patient at the time of the bite.
3. The availability or otherwise of antivenoms.
4. The clinical presentation of the patient.

Unfortunately, the reality is that identifications made by patients/others are extremely prone to error, and especially prone to the common misconception that bites by large snakes are caused by 'Papuan (Pap) blacks', a potentially lethal error if CSL blacksnake antivenom is then given erroneously to the victim of a much more dangerous Papuan taipan (*Oxyuranus scutellatus canni*).

Good descriptions of the snake can be helpful, **but always consider them with caution**:

- Large 'dark-coloured snakes with red stripes on the back' are Papuan taipans (*Oxyuranus scutellatus canni*), but **REMEMBER** the reddish dorsal stripe of the taipan may not always be seen by the patient, and failure to report it does not mean the snake was not a Papuan taipan.
- 'Small snakes with triangle-shaped heads' and short, 'sharp' tails may be death adders (*Acanthophis* spp.).
- In northern and highland provinces, a large 'white snake' or a 'pale snake with a dark head' is almost certainly a small-eyed snake (*Micropechis ikaheka*).
- **REMEMBER**: 'black snakes', whether big or small, are not necessarily genuine Papuan blacksnakes (*Pseudechis papuanus*) – there are several black or dark-coloured snakes (including taipans) that are commonly mistaken for Papuan blacksnakes.

The most important way of identifying the species responsible for a particular case of snakebite is to obtain a thorough history from the patient that includes a careful and accurate assessment of both the reported symptoms and observed signs. The clinical examination will provide you with reliable information upon which to make management decisions, including the selection of antivenom. Combined with knowledge of which species of snakes occur in your region, and what the effects of their venoms may be, it is possible to make sound presumptive identifications of the species responsible. (*See also Chapter 11 page 11.8*)

The 20WBCT should be used to determine if a coagulopathy exists, and if blood remains unclotted at 20 minutes and the bite occurred in Milne Bay, Central, Gulf or Western province, a diagnosis of envenoming by the Papuan taipan (*Oxyuranus scutellatus canni*) is extremely likely.

REMEMBER: The earliest possible administration of antivenom significantly reduces the risks of airway compromise and respiratory failure.

A further consideration is the cost and availability of antivenom. In many cases the high cost will affect which antivenoms are available, and in Papua New Guinea it is usual to give only a single ampoule of antivenom because of high costs. Further information on the procedures for the administration of antivenom is given in detail in Chapter 11 of this Handbook.

Limitations of Antivenom

Antivenom is generally very effective in the reversal of postsynaptic neurotoxicity produced by species such as death adders (*Acanthophis* spp.) and can produce remarkable improvement in the clinical situation within a short period of time for some patients.

The same cannot be said for the reversal of presynaptic neurotoxicity caused by the bites of snakes like the Papuan taipan (*Oxyuranus scutellatus canni*). Clinical experience shows that unless antivenom is given within 4 hours of a bite by this species the majority (70%) of patients will continue to deteriorate and will require intubation and ventilation. In victims of taipan bites who present late for treatment and have well established neurotoxicity, the reality is that while antivenom is of value in correcting coagulation disturbances, it is very unlikely to reverse the neurotoxicity even if given in multiple doses. Protection of the airway and planning for the necessity to provide prolonged ventilation should be important priorities.

Ancillary Drug Interventions

Anticholinesterases

Neostigmine is the only anticholinesterase that has been used for snakebite in PNG, although there are other anticholinesterase drugs available. Neostigmine inactivates the enzyme acetylcholinesterase (AChE) which is responsible for breaking down acetylcholine (ACh). As a result, ACh accumulates in the synaptic cleft, producing increased binding to receptors, and resulting in depolarisation and muscle action.

Dosage: adults 1.25-2.5mg, children 0.05-0.07mg/kg, slow iv, repeated 2-4 hourly if initial improvement in motor function is observed.

Atropine must be given in conjunction with neostigmine to counteract unwanted side effects of neostigmine, which can include bradycardia, increased salivation and sweating (*See Chapter 12 for more detailed information on anticholinesterase therapy*).

Dosage: adults 0.6-1.2mg, children 0.02mg/kg, slow iv, repeated approximately 6-hourly, depending on the reappearance of excessive salivation or sweating.