USE OF NEOSTIGMINE AFTER SNAKE BITE

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SUMMARY

Cobra venom consists of a neurotoxin which is responsible for respiratory paralysis simulating that associated with a non-depolarizing muscle relaxant. A combination of artificial respiration and neostigmine has been useful in resuscitating a child bitten by a snake.

Snakes and cretes are found all over the world except in the Arctic region, New Zealand and Ireland (Deoras, 1965). Although the number of persons bitten by snakes is not known exactly, it is estimated that, in India, about 2 million are bitten annually, of whom nearly 15,000 die (Swaroop and Grab, 1954; Ahuja and Singh, 1956; Banerjee and Bhattacharya, 1960; Minton, 1963; Santosh and Usagaonkar, 1968). The global death rate for snake bite is about 30,000 per annum, the tropical regions of Asia and Africa alone contributing nearly 65% of the mortality because of the presence of poisonous snakes in these zones. Although the death rate from snake bites is 5.4% in India, this relates to human lives only as there are no data about the losses to live-stock and other domestic animals (Deoras, 1965).

The treatment of snake bite is controversial because there is no completely successful method (Lockhart, 1965). The management of snake bite poisoning involves first aid methods (tourniquet, excision, incision and suction) and specific therapy (antivenom serum and antibiotics). Cryotherapy with refrigeration for the extremities is efficient in controlling enzyme destruction of tissues following a bite by the rattlesnake (Mullins, 1960; Lockhart, 1965).

It was demonstrated by Kellaway and Holden (1932) that snake venom has an action on the neuromuscular junction which resembles a non-depolarizing block, thereby producing skeletal muscular paralysis. This led to the belief that artificial ventilation should form an important part of therapy. This was shown to be so by Gode, Tandon and Bhide (1968) in experimental cobra envenomation in dogs and was confirmed by Mehta, Kelkar and Parikh (1968) in human subjects. It was postulated also that neostigmine may be of help in resuscitating these patients (Harrison et al., 1966) and this has been confirmed by other workers (Ghosh and Mandal, 1964; Santosh and Usagaonkar, 1968; Banerjee et al., 1972).

We present here a case of snake bite successfully treated with artificial ventilation and neostigmine.

CASE REPORT

The anaesthetist received an urgent call to a 10-yr-old child with marked cyanosis and no respiratory activity. Ventilation was being assisted manually. Immediate tracheal intubation was performed and oxygen-enriched air was administered with the help of an Ambu resuscitator. Within a few minutes the child's colour improved. However, respiration was inadequate still and continued artificial ventilation was required.

The child, who had been in good health, had been bitten on the dorsum of the left foot by a snake 3-4 h earlier. His father had applied a tourniquet immediately and made an incision on the dorsum of the foot. The child was then rushed to a hospital, about 50 km from our hospital, where he was given tetanus toxoid and antibiotics.

On clinical examination, the heart rate was 160 beat. min⁻¹. The pupils were dilated and reacted sluggishly to light, and the patient was in a state of cardiovascular collapse. Dextrose in saline, hydrocortisone acetate, mephenteramine and sodium bicarbonate were administered i.v. Anti-snake venom was given i.v. However, there was no improvement in the child's respiration and assisted ventilation was continued with an Ambu bag.

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As respiratory failure associated with neurotoxin was considered it was thought that neostigmine might be effective. Initially, neostigmine 0.5 mg, diluted to 5 ml with distilled water, was given slowly i.v. After a few minutes the heart rate was 120 beat. min⁻¹ and there was a marked improvement in respiration. Encouraged by this response, we repeated the same
dose 10 min later and again after a further 20 min. By this time the heart rate was 90 beat.min⁻¹ and respiration was adequate. The tracheal tube remained in position for a further period of 2 h. When the child was unable to tolerate the tube it was removed following suction to the throat. Thereafter respiration remained satisfactory; the child remained in hospital for the treatment of cellulitis.

Neither haematuria nor bleeding from any other site were noted. On the day following the bite, the bleeding time was 1 min 15 s and the clotting time was 6 min. The child has since successfully undergone desloughing and skin grafting procedures.

**DISCUSSION**

Snake venom is a highly concentrated digestive juice which, on drying, forms fine needle-like crystals. The crude cobra venom consists of three active ingredients (Kellaway and Holden, 1932; De and Ghosh, 1937; Ghosh, De and Choudhary, 1941; Sarkar, 1951; Lee and Peng, 1961; Meldrum, 1965; Vick, Cinechta and Polley, 1965):

(a) A haemolysin. Phosphatidase produces enzymatic destruction of cell walls, tissues and the endothelium of the blood vessels. Consequently there is lysis of red blood cells, haemorrhage and acute haemolytic anaemia.

(b) A cardiotoxin. The effect of this fraction has been studied extensively (for example: Chopra and Ishwariah, 1931; Gottdenkar and Wachsteinum, 1940; Sarkar, 1947, 1948, 1951; Sarkar and Maitra, 1950; Bhanganada and Perry, 1963). It was found that small doses of venom increased the force of myocardial contraction, cardiac output and arterial pressure, while with large doses there was depression of the myocardium, leading to asystole. The hypotension which occurs may be a result of a direct depressant effect on myocardium, depression of the vasomotor centre (Chopra and Ishwariah, 1931) or paralysis of the peripheral vasculature (Bhanganada and Perry, 1963).

(c) A neurotoxin. This acts on the neuromuscular junction, producing a curare-like effect and muscle paralysis (Kellaway and Holden, 1932; Lee and Peng, 1961; Vick, Cinechta and Polley, 1965). However, there are distinct differences between the actions of the neurotoxin and those of curare. The neurotoxin is slower in onset and the block cannot be antagonized by washing out the end-plate. Also, the block is sustained for several hours after exposure to toxins. The neurotoxin block may be antagonized or decreased by anticholinesterases as long as it is only partial. However, anti-cholinesterases have very little effect on a fully established block *in vitro* (Meldrum, 1965). Paralysis occurs in the muscles of the mouth, throat and breathing in that order (Mehta, Kelkar and Parikh, 1968). The neurotoxin fraction of the venom is relatively heat-stable (Sarkar, 1947) and it is thought that heating crude venom solution at 90 °C for 30 min leaves the neurotoxin unaffected while destroying the other fractions (Ramachandra, Kaul and Gode, 1974).

The other enzymes in the venom are: proteases, erepsin, cholinesterase, hyaluronidase (a solubilizing enzyme which acts on the intracellular substance of the connective tissue facilitating spread of the toxin), ribonuclease and desoxyribonuclease, and ophio-oxidase (which promotes autolysis and putrefaction (Porges, 1953)).

The histopathological lesions depend upon the dose of venom and consist of changes in Nissls granules, fragmentation of the reticulum of the nerve cells, opacity of the nuclei and the fragmentation and swelling of the nucleoli. Sometimes acute granular degeneration may be seen also (Mehta, Kelkar and Parikh, 1968).

Without treatment, death occurs from 20 min to 6 h after a bite, depending upon the site, the amount of venom at the site and the rate of absorption. It is believed that 12 mg of dried cobra venom may be fatal (Deoras, 1965).

Cardiovascular collapse may have been caused by the cardiotoxin (Chopra and Ishwariah, 1931; Gottdenkar and Wachsteinum, 1940; Sarkar, 1947, 1948, 1951; Sarkar and Maitra, 1950; Bhanganada and Perry, 1963). It was found that small doses of venom increased the force of myocardial contraction, cardiac output and arterial pressure, while with large doses there was depression of the myocardium, leading to asystole. The hypotension which occurs may be a result of a direct depressant effect on myocardium, depression of the vasomotor centre (Chopra and Ishwariah, 1931) or paralysis of the peripheral vasculature (Bhanganada and Perry, 1963).

In the present case report, cyanosis was observed nearly 3.5 h after the bite. Although first aid had been given initially it seems likely that some toxin remained and, after the release of the tourniquet, was absorbed slowly producing a neuromuscular block and resulting in respiratory paralysis similar to that following a non-depolarizing muscle relaxant (Kellaway, Cheny and Williams, 1932).

Doubt exists, however, as to whether the neuromuscular block is a result of neurotoxin or antivenom serum (Mehta, Kelkar and Parikh, 1968). Since, in this patient, the antivenom was given after admission to the hospital, when the patient was already in respiratory failure, it seems likely that the neuromuscular block was caused by the neurotoxin. Neurological assessment of such patients is difficult
as there is paralysis of all the cranial and peripheral nerves (Harrison et al., 1966). Since the ocullomotor nerves are affected also, both light and accommodation reflexes are lost and widely dilated pupils need not indicate intracranial pathology. In addition, it is difficult to assess levels of consciousness since the patient cannot react appropriately to painful stimuli.

Since the site of action of the toxin is now known to be at the neuromuscular junction, it follows that artificial ventilation should form part of the treatment (Gode, Tandon and Bhide, 1968; Mehta, Kelkar and Parikh, 1968). In this case the child's general condition improved after artificial ventilation with oxygen-enriched air.

The therapeutic response to neostigmine depends upon the following factors (Banerjee et al., 1972):
(a) Degree of neuromuscular block (whether partial or complete)
(b) Blood concentration of neostigmine and its continued maintenance until complete neutralization of the neurotoxin
(c) The dose of cardiotoxin absorbed which is totally unresponsive to the anticholinesterase

In earlier studies the usefulness of neostigmine has been demonstrated by improved survival and more rapid recovery (Santosh and Usagaonkar, 1968; Banerjee et al., 1972). Our findings are in agreement with earlier observations that the combination of neostigmine and atropine sulphate is safe, although in some cases the heart rate was in excess of 160 beat. min⁻¹.

It would appear that the dose of venom absorbed was small, as only 1.5 mg of neostigmine was required to neutralize the effects of the toxin and it was not found necessary to continue the drug treatment. The immediate application of the tourniquet and the incision of the site of bite by the father appears to have been a contributory factor in the low absorption of venom.

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REFERENCES

**USAGE DE LA NEOSTIGMINE APRES UNE MORSURE DE SERPENT**

*RESUME*

Le venin du cobra contient une neurotoxine qui provoque une paralysie respiratoire semblable à celle associée à un relaxant musculaire non dépolarisant. La combinaison de respiration artificielle et de néostigmine a permis de réanimer un enfant qui avait été mordu par un serpent.

**VERWENDUNG VON NEOSTIGMIN NACH SCHLANGENBISS**

*ZUSAMMENFASSUNG*

Kobragift besteht aus einem Neurotoxin, das eine sonst durch ein nichtdepolarisierendes Muskelentspannungsmittel hervorgerufene Atmungslähmung bewirkt. Eine Verbindung von künstlicher Atmung und Neostigmin erwies sich bei der Wiederbelebung eines von einer Schlange gebissenen Kindes als nützlich.

**EMPLEO DE NEOESTIGMINA DESPUES DE PICADURA DE VIBORA**

*SUMARIO*

El veneno de cobra consiste de una neurotoxina que es responsable de parálisis respiratoria, simulando aquél asociado con un relajador de músculo no despolarizante. Una combinación de respiración artificial y neostigmina ha sido útil en la resucitación de un menor picado por una vibora.
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References
Tinker, J.H., and Michenfelder, J.D., Anesthesiology, 1976, 45, No.3, 340

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