Neostigmine in the Neuroparalytic Effects of Snake Bite

INTRODUCTION:

Snake venom with its many toxic components produce brain stem lesions and neuromuscular paralysis resulting in respiratory failure and death. In north India the common poisonous snakes are of elapidae family (cobra and Krait), though poisonous snakes of viperinae family are also found (Wig and Vaish, 1960; Sarangi et al, 1977).

While in vipers snake bites local lesions along with different systemic effects like haemorrhage, shock and haemolysis are important, in the elapidae bites the most common cause of death is neuromuscular paralysis and brain stem lesion. These effects so much mimic the myasthenic features that the authors were prompted to use neostigmine in such cases and having observed a dramatic effect of this therapy has extended the regimen to 65 cases where the clinical features indicated envenomation and neuromuscular paralysis. The results were compared with the conventional therapy and the analysis appear so significant that the authors recommend a routine use of neostigmine in snake bite cases in this region.

METHOD AND MATERIAL:

All cases included in this study were admitted to Darbhanga Medical College Hospital between February 1975 to March 1977.

* Resident Medical officer
** Assistant Professor of Medicine
*** Professor of Medicine, Darbhanga Medical College, Laheriasari, North Bihar, India.
Those patients who were admitted on Thursdays received Neostigmine therapy along with conventional treatment while those admitted on other days of the week were put on conventional therapy alone.

The treatment regimen thus followed were marked as Regimen I for conventional therapy consisting of 20 ml of lipohlized polyvalent antivenine + 40 mg of Pheniramine maliate + 8 mg of bitamethasone and other supportive therapy like antibiotic, oxygen and artificial respiration when necessary and Regimen II for those which in addition to above, received Neostigmine and Atropine sulphate, the doses of which varied from case to case.

The severity of snakebite was graded as mild, moderate, and severe on the basis of the points arbitrarily allotted to features of envenomation as will be clear from Table I. Only those cases were put on active treatment who showed signs of envenomation. A total of 35 cases received conventional therapy while another 65 cases received in addition, Neostigmine.

**TABLE I**

Points allotted to different features of envenomation.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2</td>
</tr>
<tr>
<td>Aphonia</td>
<td>3</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>3</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3</td>
</tr>
<tr>
<td>Apnoea and laboured respiration</td>
<td>4</td>
</tr>
<tr>
<td>Circulatory failure</td>
<td>4</td>
</tr>
<tr>
<td>Coma</td>
<td>4</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

On the basis of the points scored by any given case they were graded as mild (score 1 to 5), moderate (6 to 10) and severe (11 and over).
TABLE II
Showing distribution of cases and the result of therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total no. of cases</th>
<th>Survived</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen I</td>
<td>35</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(80%)</td>
<td>(20%)</td>
<td></td>
</tr>
<tr>
<td>Regimen II</td>
<td>65</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(93.84%)</td>
<td>(6.15%)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE III
Showing distribution of cases under different degree of severity and the outcome of therapy

<table>
<thead>
<tr>
<th>Conventional therapy (Regimen I)</th>
<th>Mild severity</th>
<th>Moderate severity</th>
<th>Marked severity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>Survival</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(75%)</td>
<td></td>
<td>(66.66%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6.66%)</td>
<td>(25%)</td>
<td>(33.33%)</td>
<td></td>
</tr>
</tbody>
</table>

Conventional + Neostigmine (Regimen II)

| Total cases                      | 24            | 19                 | 22              | 65    |
| Survival                         | 24            | 18                 | 19              |       |
|                                  | (94.74%)      | (86.37%)           |                 |       |
| Death                            | nil           | 1                  | 3               |       |
|                                  | (5.26%)       | (13.63%)           |                 |       |

There is a marked reduction in death rate irrespective of severity under regimen and even in severe cases the difference is significant on comparison.

DISCUSSION
Though the world mortality from snake bite has been as high as 30–40 thousand year (Wallace, 1977) and even though in Indian subcontinent alone the figure is

JNMA April-June 1979 19
15-20 thousand deaths per year (Chaterjee 1971) no serious attempt has been made over these years to understand the physiopathology of snake venom and even slower progress has been in therapy.

In the Indian subcontinent most of the deaths are ascribed to bites from snakes of elapidae family (Cobra and Krait) though bites from snakes of viperinae family are also common (Wig and Vaish, 1960; Sarangi et al, 1977).

Respiratory paralysis is the prime cause of death in our part of the country though death from haemorrhage and shock from renal failure and occasionally from anaphylaxis may be encountered (Ellis et al, 1965; Abraham et al, 1973; Chugh et al, 1975; Das et al, 1976; Sarangi et al, 1977).

The venoms of most of the species which have been analysed contain a mixture of several toxic proteins and enzymes with many complicated pharmacologic action. While Hyaluronidases present in most venoms lead to rapid absorption, proteases cause local inflammation and necrosis; phospholipase A alters membrane permeability and releases histamine; Phosphodiesterase is responsible for hypotension and Esterases found in viper venoms liberate Bradykinin (Zeller, 1951; Braganca & Quastel, 1953; Braganca & Patel, 1965; Minton Jr., 1975; Wallace, 1977).

About 40 toxins have been isolated from elapid and sea snake venoms. The cobrotoxin from Chinese cobra have yielded peptide toxins of 7000 molecular weight containing 61 to 74 amino acids linked by disulfide bonds. These produce a nondepolarising neuromuscular block by their action on the postjunctional membrane of the motor end plate. Some of these peptide also produce neuromuscular blockade by reducing acetylcholine output at the presynaptic nerve terminals (Minton Jr., 1975).

The cholinesterase, nucleotidases and a potent inhibitor of cytochrome oxidases may easily interfere with the cellular metabolism and the brainstem lesion in snake bites can be easily imagined. Though many of these peptide toxins and enzymes may be present in a particular venom, the elapidae venom is predominantly neurotoxic and the respiratory paralysis that follows envenomation is caused by damage to the brain centers and a curare like interference with transmission at the neuromuscular junction.
Only those cases who had ptosis, strabismus, dysphagia with speech defects, drooling of saliva and difficulty in respiration were included in this study. While all the patients received 45 mg. of pheniramine maleate, 8 mg. of Betamethasone intravenously along with 20 c.c. of polyvalent antivenine 65 cases received along with the above therapy varied amounts of neostigmine over 48 hours period.

Atropine sulphate 0.6 mg. was also given intravenously immediately before the dose of (0.5 mg.) neostigmine. This dose of neostigmine was repeated in any given circumstance every 10 minutes depending on the response. Usually the dose of neostigmine varied from 1.5 mgm. in the first hour to a total of 4.5 mgm. to 6 mgm. over 48 hours, 15 mgm. being repeated according to the need and response and later every 4 to 6 hours. Atropine sulphate was given in dose of 0.6 mg. repeated every 6 to 8 hours neostigmine therapy was continued. Pheniramine maleate was repeated only 12 hourly and Betamethasone only occasionally.

The dramatic effect observed on neostigmine therapy confirms that this drug has definite role to play because of its anticholinesterase action and works by restoring acetylcholine at the myoneural junction.

Seven deaths under conventional therapy could have been prevented if this neuromuscular paralysis and respiratory paralysis could have been controlled by judicious and timely administration of neostigmine.

The significant difference in the outcome of neostigmine group of cases (Table I, III) is an ample evidence that in this region, whenever features of envenomation become apparent, neostigmine should be routinely used.

The authors however feel that polyvalent antivenine, corticosteroids, antihistamines and other supportive measures should not be omitted even with neostigmine because of different pharmacologic effects of both the venom and these drugs.

SUMMARY:

Neostigmine therapy, was added to the conventional therapeutic regimen in 65 cases of snake bite. The neuromuscular paralysis, the principal defect in these cases improved dramatically.

JNMA April-June 1979
Comparison between conventional therapy alone and one with neostigmine addition revealed significant reduction in death rate (20% vs. 6.15%).

The authors recommend routine use of neostigmine in any case of snake bite showing slightest signs of envenomation.

ACKNOWLEDGEMENT:

We are greatly thankful to the Superintendent, D. M. C. H. for permission to publish the report of these cases. We shall fail in our duty if we did not extend our gratitude to Dr. S. A. Chaitale, National Medical Library, New Delhi for promptly supplying us with the reprints.

BIBLIOGRAPHY:


   "A profile of snake bite poisoning with special reference to haematological, renal, neurological and Electrocardiography abnormalities"

   "Harrison's principles of internal medicine",
   International student edition, MacGraw Hill,

   "Management of snake bite cases"
   J. I. M. A., 45; 654-659.

5. Ellis E. F. and Smith, R. T.
   "Systemic anaphylaxis after rattle snake bite"

   "Neurotoxic snake bite Dramatic recovery following neostigmine therapy"

   "Acute renal failure following snake bite"

   "Glycoproteins as components of the lethal fraction in cobra venom (Naja naja)"
   Canadian Journal of Biochemistry, 43.915-921.
   "Enzyme inhibition by snake venoms",

    "Venom diseases", Text Book of Medicine; Cecil-Loeb,
    Ed. 14th, W. B. Saunders Company, Philadelphia,
    Igaku Shpin Ltd., Tokyo, 88–92.
    In "The Enzymes", 1, Part 2, p.987 Ed. by
    Sumner, J. B. & Myrback, K., New York,
    Academic Press
    "Neurotoxic snake bite leading to respiratory arrest",


12. Abraham, P. T. and Mathew, A.
    (1973)

---

Entobex

dual-action amoebicide

- effective against both amoeba and bacteria
- destroys entamoeba histolytica at all stages of development
- provides high luminal concentration
- effective in "cyst passers"
- excellent clinical record
- well tolerated

CIBA-GEIGY of India Limited, Bombay 400 020 (Licensed Users of Trade Mark)