NEUROMUSCULAR BLOCKING AND HYPOTENSIVE ACTIONS OF STREPTOMYCIN, AND THEIR REVERSAL

BY

K. PANDEY, S. KUMAR AND R. P. BADOLA

Departments of Anaesthesiology and Physiology, King George's Medical College, Lucknow, India

SUMMARY

Large doses of streptomycin injected in 20 dogs anaesthetized with chloralose or pentobarbitone caused neuromuscular blockade, as judged by the response of the tibialis anterior muscle to peripheral nerve stimulation. Marked arterial hypotension invariably occurred. In all of four dogs pholedrine restored and maintained blood pressure, but the amplitude of respiration and tibialis twitch still decreased with large doses of streptomycin. Neostigmine led to a slow and incomplete recovery of twitch response and little increase in blood pressure. Calcium chloride alone, and after neostigmine, caused a quick and complete recovery of twitch response and restored the blood pressure. It is suggested that small doses of calcium chloride may be of use clinically when hypotension and neuromuscular block occur due to large doses of streptomycin.

Streptomycin has been shown to possess a neuromuscular blocking action (Brazil and Corrado, 1957; Bezzi and Gessa, 1959, 1961; Timmerman, Long and Pittinger, 1959). Patients being treated by daily intramuscular injections of streptomycin have been reported to have developed extreme muscular weakness and blurring of vision (Loder and Walker, 1959). Introduction of streptomycin into the peritoneal or pleural cavity before wound closure has given rise to prolonged respiratory depression in the postoperative period in many surgical cases (Bush, 1961; Benz, Lunn and Foldes, 1961; Fisk, 1961; Bodley and Brett, 1961; Emery, 1961). In the cases reported by Fisk (1961) a precipitous fall in blood pressure was also noted in addition to marked respiratory depression.

Brazil and Corrado (1957) in their experimental work found that calcium chloride and neostigmine methylsulphate antagonized the neuromuscular blockade produced by streptomycin. Loder and Walker (1959) reported immediate improvement in muscle power and restoration of vision by administration of neostigmine methylsulphate. But Bush (1961), Fisk (1961) and Bodley and Brett (1961) have reported very slight or negligible improvement after administration of neostigmine in some of the surgical cases in whom respiratory depression had developed after instillation of streptomycin in the peritoneal cavity.

In view of these conflicting reports about the efficacy of antidotes, the present work was undertaken to study the effects of relatively large doses of streptomycin on muscle power, respiration and blood pressure, and also to test the efficacy of the agents advocated for the reversal of these effects.

METHOD

The experiments were performed on twenty healthy mongrel dogs weighing between 9 and 14 kg and anaesthetized with chloralose 100 mg/kg (fifteen dogs) or pentobarbitone sodium 25 mg/kg (five dogs). The tibialis anterior muscle was exposed and its tendon of insertion was divided and tied to an isometric lever to record its contractions kymographically. When tying the muscle the resting tension was so adjusted as to cause as little deflection of the writing point of the lever as possible. This tension was maintained constant throughout the experiment by proper fixation of the tibia and the isometric lever bracket. The deflection of the writing point of the lever was

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Effect of large doses of streptomycin on the blood pressure and the twitch response in anaesthetized dogs and the effect of neostigmine methysulphate (Prostigmine).

### Table I

<table>
<thead>
<tr>
<th>Dog</th>
<th>Blood pressure (mm Hg)</th>
<th>Twitch response</th>
<th>Antidote</th>
<th>Initial movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>200</td>
<td>Ca</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>240</td>
<td>Ca</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>200</td>
<td>Ca</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>220</td>
<td>Ca</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>200</td>
<td>Ca</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>200</td>
<td>Ca</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Indicates experiments under pentobarbitone sodium anaesthesia. All other dogs received chloralose anaesthesia.*

**Antidotes**

- **V.G.R.** = Very gradual recovery
- **Q.R.** = Quick recovery
- **Q.C.R.** = Quick and complete recovery
- **R.R.A.** = Rate of recovery accelerated
- **N.F.T.** = No further improvement
- **S.F.I.** = Slight further improvement

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The last four dogs were given 4 mg of pholedrine sulphate to counteract the fall of blood pressure. Complete abolition of lever movement was not attempted before injection of antidotes.
1 cm per every 200 g of an applied static weight throughout the range of recorded twitches.

The nerve supplying the muscle was also dissected out and divided. The peripheral end of the nerve was used for indirect stimulation by square wave pulses at 50 volts and of 0.5 m.sec duration through platinum electrodes. An electronic stimulator was employed for delivering the pulses.

Carotid artery blood pressure and respiratory excursions were also simultaneously recorded by cannulating the carotid artery and the trachea and connecting the cannulae to a U-tube mercury manometer and a Marey's tambour, respectively. The femoral vein was used for administering the drugs through an indwelling cannula.

Streptomycin was injected in quantities of 200 or 100 mg while the muscle was being stimulated indirectly at the rate of 1/sec. Initially, the doses of streptomycin were designed to produce the maximum fall in blood pressure. When the lowest blood pressure was attained, further doses of streptomycin were given to completely abolish the movements of the isometric lever by the muscle.

In eight dogs, after abolishing the isometric lever movement, 200–800 mg of calcium chloride was first administered as an antidote. This was followed by 1–1.5 mg of neostigmine methylsulphate after some time in four dogs.

Similarly, in eight other dogs 1–1.5 mg of neostigmine was given first as an antidote and this was followed by 200–400 mg of calcium chloride in five dogs.

In four dogs, pholedrine sulphate 4 mg was injected after a few doses of streptomycin, to reverse the hypotension; further doses of streptomycin were then given. In these four dogs complete abolition of the isometric lever movement was not attempted. However, calcium chloride and/or neostigmine were also given as antidotes in these dogs.

All dogs receiving neostigmine methylsulphate were given atropine sulphate 0.65 mg either at the beginning of the experiment or before injection of neostigmine.

RESULTS

Observations on the effects of streptomycin on blood pressure and the tibialis anterior twitch response are summarized in table I, as is also the quality of reversal of these effects by neostigmine and calcium chloride.

Effects on the contractions of the tibialis anterior.

A gradual decrease in the amplitude of the muscle twitch was observed as the amount of streptomycin injected was increased. A dose of 100–200 mg/kg of streptomycin base was needed to abolish the movements of the isometric lever by the muscle when indirectly stimulated at the rate of 1/sec (figs. 1 and 2).

Effects on respiration.

Initially an increase in frequency and amplitude of respiratory excursions was observed in every experiment (figs. 1, 2, 3 and 4). Then, as more and more streptomycin was injected, the amplitude markedly decreased. The increase in frequency of respiration was persistent in most experiments (figs. 1 and 2). There was a tendency for a partial recovery of the amplitude of respiration even while the block of tibialis anterior was progressing.

Cyanosis was never observed in any experiment. Neither was apnoea seen with doses of streptomycin sufficient to abolish the movement of the isometric lever by tibialis anterior twitch response.

Effect on blood pressure.

A remarkable fall in blood pressure was the earliest manifestation of intravenous injection of streptomycin. The mean blood pressure fell to 40–90 mm Hg from a resting level of 90–160 mm Hg (figs 1, 2, 3 and 4). The dose of streptomycin base per kg body weight producing the maximum fall in blood pressure, ranged between 22.2 to 127.3 mg. Once this maximum drop in blood pressure had occurred in any particular experiment, subsequent injections of streptomycin caused no further fall.

Pholedrine sulphate 4 mg restored and maintained the blood pressure above the control level (fig. 3). It also prevented fall in blood pressure in response to subsequent doses of streptomycin.

Reversal by neostigmine methylsulphate and calcium chloride.

Neostigmine methylsulphate produced a slow and incomplete recovery of the twitch response of the tibialis anterior. It produced little increase in blood pressure.
Calcium chloride, either given alone or after neostigmine, produced a quick and complete recovery of the twitch response of tibialis anterior (fig. 3). The restoration of blood pressure by calcium chloride was instantaneous. Neostigmine given after calcium chloride produced no further improvement.

DISCUSSION

From the observations in this study it is clear that neuromuscular block and severe hypotension are invariable features of acute streptomycin toxicity in dogs. Similar observations have been made by Brazil and Corrado (1957).

That hypotension produced by streptomycin is due to a ganglioplegic action has been proved beyond doubt by Corrado (1958). It is also evident from our observations that the fall in blood pressure is not the cause of diminution of muscle power because maintenance of blood pressure at control levels by giving pholedrine sulphate did not prevent the diminution of amplitude of twitch response of tibialis anterior by subsequent doses of streptomycin.

The effects of streptomycin on respiratory excursions have not been of a constant pattern in our experiments. This inconstancy of pattern may be explained on the basis of the assumption that respiratory activity was influenced by a variety of factors such as (i) reflex effects due to fall or rise of blood pressure, (ii) reflex and central actions of hypoxia and hypercarbia, and (iii) partial paralysis of respiratory muscles due to neuromuscular blockade. Molitor and associates (1946), in animals, noted an increase in frequency and depth of respiration after small intravenous doses (0.1-2 mg/kg) with respiratory paralysis and death after large doses (70 mg/kg) of streptomycin.

From the illustrations it might appear that the paralyzing action of streptomycin on respiratory muscles is not as marked as it is on tibialis anterior. Under the conditions of our experiments this would not be a valid conclusion, because the activity of the tibialis anterior was being recorded through a lever which required a weight of 200 g to move its writing point by 1 cm while the respiratory excursions were recorded by an arrangement which was almost free from any such instrumental resistance.

It is probable that the ominous combination of severe hypotension with partial respiratory muscle paralysis is the real cause of trouble in most of the reported cases of respiratory inadequacy after intraperitoneal and/or intrapleural instillation of streptomycin during operation.

Clinically, streptomycin is likely to lead to frank neuromuscular block only in those cases in whom a large amount of this drug is applied at sites from which it may be quickly absorbed. For example, in one case reported by Fisk (1961), 5 g of streptomycin was put in the peritoneal cavity and another 5 g was put in the pleural cavity at the end of an operation for stricture of the lower end of the oesophagus. This case had also been given d-tubocurarine (Bezzi and Gessa, 1961), and the neuromuscular blocking action of streptomycin has been shown to be potentiated by d-tubocurarine.

Doses of 1-2 g of streptomycin in absence of potentiating factors like d-tubocurarine or ether may be expected to cause neuromuscular block in small children or infants. Bush (1961) has reported one such case of a 6-months-old infant who was given 1 g of streptomycin intraperitoneally before wound closure after rectosigmoidectomy. Another situation where streptomycin in small doses is likely to produce muscular paralysis is the one where the patient is already in a state of severe electrolyte imbalance. As hinted by Bush (1961), one wonders whether the six cases of neostigmine-resistant curarization reported by Hunter (1956) had received intraperitoneal streptomycin, or not!

Neuromuscular blockade apart, the hypotension, which may be quite severe, may itself be a serious complication of instillation of large doses of streptomycin at sites from which it is likely to be quickly absorbed. The amount of streptomycin needed for production of profound hypotension is much less, as is evident from our experiments. Calculated on the basis of 40 mg/kg an adult weighing 50 kg may develop severe hypotension after 2 g of streptomycin if it enters into his circulation quickly. Such a dose of streptomycin is very commonly administered especially in cases of peritonitis who may already be having some degree of hypotension. The effect of sudden and severe hypotension in these cases may well be imagined.
The quality of reversal of neuromuscular block and hypotension by neostigmine methylsulphate and calcium chloride in this study deserves special notice. Brazil and Corrado (1957) stated that both these drugs were capable of completely reversing the neuromuscular block produced by streptomycin although the action of neostigmine methylsulphate "occurred more slowly and gradually". However, from the present study it is evident that the reversal of neuromuscular block by neostigmine methylsulphate is not only slow and gradual, but is also incomplete. Administration of calcium chloride, on the other hand, either alone or after neostigmine methylsulphate, always quickly and completely reverses the neuromuscular block. Neostigmine methylsulphate has a still slower action in reversing the hypotension. Calcium chloride, however, corrects this in a dramatic manner. On the basis of these observations therefore, calcium chloride in small doses (200–500 mg) appears to be the drug of choice for the treatment of cases manifesting acute streptomycin toxicity in the form of neuromuscular blockade and arterial hypotension.

REFERENCES


BLOQUAGE NEURO-MUSCULAIRE ET EFFET HYPOTENSIF DE STREPTOMYCINE ET LEUR INVERSION

SOMMAIRE

D'importantes doses de streptomycine injectées à 20 chiens anesthésiés par pentobarbiturate ou chloralose provoquèrent un blocage neuro-musculaire reconnu par réaction du muscle tibial antérieur à une stimulation des nerfs périphériques. Il y eut alors invariablement du l'hypotension artérielle assez marquée. Chez tous les 4 chiens ainsi traités la pholédrone remit ensuite maintintà la normale la tension, mais l'amplitude de respiration et la contraction brusque de la tibiale continua encore à diminuer sous l'effet de fortes doses de streptomycine. La néostigmine eut pour résultat un rétablissement lent et incomplet de la réaction de contraction et une augmentation faible de la tension artérielle. Le chlorure de calcium seul et après néostigmine provoqua un rétablissement rapide et complet de la réaction de contraction et de celle de la tension artérielle. Les auteurs pensent que de faibles doses de chlorure de calcium peuvent être utiles cliniquement lorsque de fortes doses de streptomycine provoquent de l'hypotension et du blocage neuro-musculaire.

NEUROMUSKULÄRE BLOCKADE UND BLUTDRUCKSENKENDE WIRKUNG VON STREPTOMYCIN UND DIE UMKEHRUNG DIESER WIRKUNGEN

ZUSAMMENFASSUNG