

Administration of depolarizing muscle relaxants after non-depolarizer reversal: when is it safe?

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Summary

In the light of studies on the duration of action and pharmacokinetics of intravenous neostigmine, it is recommended that, depending upon the dosage administered, at least 1 hour should elapse before a depolarizer can safely be given after neuromuscular reversal with neostigmine, and at least 90 - 120 minutes after reversal with physostigmine. It is suggested that a diluted test dose of depolarizer be given first, and its effect monitored with a peripheral nerve stimulator because fasciculations will not occur.

S. Afr. med. J., 61, 583 (1982).

The use of depolarizing muscle relaxants to facilitate intubation, followed by non-depolarizers for continued relaxation, is safe clinical practice, provided that the return of neuromuscular activity before administration of the non-depolarizer is either monitored with a peripheral nerve stimulator or assessed visually. However, administration of depolarizers *subsequent* to reversal of non-depolarizer neuromuscular blockade is unusual, and in standard texts no rules or recommendations are laid down should such administration be necessary.

The following case report illustrates a problem which may arise in this respect.

Case report

A 56-year-old White male presented for major excision of a large, neglected rodent ulcer on the chin and reconstructive facial surgery. He had undergone an uneventful prostatectomy 5 years previously. He admitted to excessive cigarette smoking (30/d) and consequently suffered from a chronic cough. He became dyspnoeic on mild exercise and complained of vague chest pains. The history was otherwise negative.

Examination disclosed an overweight, anxious individual with a short thick neck. Some upper incisors had been extracted. He was normotensive and there were clinical signs of emphysema.

Omnopon 15 mg and promethazine 25 mg were administered intramuscularly 1 hour before induction. Intravenous infusion of a balanced physiological salt solution (Hidroliet; Sabax) was commenced and an ECG monitor connected. Anaesthetic induction was with fentanyl 100 µg and droperidol 5 mg,

followed by thiopentone 4 mg/kg and alcuronium 0,25 mg/kg, and mask ventilation with N₂O and O₂ in a 1 : 1 ratio (total flow 6 l/min). Intubation was difficult because of lack of mobility of the neck and irregular teeth. A metal tooth guard, such as is used during oesophagoscopy, was necessary. Intubation was eventually performed blind with the aid of a pliable introducer because the vocal chords could not be visualized.

Anaesthesia was maintained with N₂O and O₂ in a 1 : 1 ratio (4 l/min), with enflurane 0,8 - 1% and mild hyperventilation. The operation lasted 90 minutes and was uneventful. At the termination of anaesthesia, glycopyrrolate 0,4 mg and neostigmine 2,5 mg were administered for neuromuscular reversal. Extubation was uneventful.

Immediately after the patient's arrival in the recovery area, the formation of a large haematoma under the skin flaps was noted. This required immediate drainage and re-establishment of haemostasis, since the viability of the skin flaps would otherwise have been jeopardized. The surgeon requested the return of the patient to the operating room.

Re-intubation was obviously mandatory. After delaying as long as possible, for reasons to be discussed later, induction following pre-oxygenation was with alphaxalone 50 µl/kg. Relaxation was achieved with suxamethonium chloride 100 mg diluted to 10 ml. Of this, 5 mg was administered intravenously and neuromuscular function assessed with a peripheral nerve stimulator. Since no fasciculations or relaxation occurred 95 mg suxamethonium chloride was administered. Intubation was performed as before and the rest of the procedure was uneventful, anaesthesia being maintained with N₂O and O₂ in a 1 : 1 ratio and enflurane (3 - 1,5%); spontaneous respiration resumed 7 minutes after administration of the depolarizer.

Discussion

For the second procedure, one had a number of options:

Local anaesthesia was considered impracticable owing to the extent of the procedure and the fact that surgical incision, with raising of skin flaps, had already been performed (infiltration would probably not have been effective).

Mask anaesthesia. A face mask would have interfered with surgery and been hazardous with an already difficult airway.

Endotracheal anaesthesia. Since endotracheal intubation was considered mandatory, two possible methods presented: awake intubation and general anaesthesia. Awake intubation was considered impossible in the light of the difficulty in intubating this patient even when adequately relaxed.

General anaesthesia was therefore deemed necessary, but the choice of relaxant posed a problem, since neostigmine must still have been present at the neuromuscular junction. Neostigmine antagonizes the enzyme acetylcholinesterase at the neuromuscular junction, thereby allowing acetylcholine to accumulate and displace non-depolarizing relaxants in a competitive fashion. However, Miller¹ stated that, even with a normal head-lift and hand-grip test, residual occupation of the neuromuscular junction by a non-depolarizer may be as high as 33%. The sensitivity of a patient to a non-depolarizing relaxant is

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therefore not predictable in these circumstances, and adequate relaxation may only be obtained by an overdose. Subsequent reversal would then be unreliable. The duration of the second procedure was also uncertain.

Neostigmine also has an inhibiting effect on pseudocholinesterase, and therefore delays the hydrolysis of suxamethonium chloride, thus making the duration of block unpredictable as well as possibly altering the pattern of block (development of a phase II or non-depolarizing block is more likely with prolonged action of depolarizer).

It is clear from the foregoing discussion that both types of neuromuscular relaxant presented certain problems in this clinical situation. However, the most acceptable technique seemed to be the use of a depolarizer. Surgery was delayed as long as possible (1 hour) and suxamethonium given as described earlier. The rationale of this approach is taken from the data regarding the duration of action of intravenous neostigmine. The standard of pharmacology and anaesthesia texts give us little information on this. Miller *et al.*² assessed comparative times to peak effect and duration of action of intravenous neostigmine and physostigmine in humans and in cats, using different dosages. They designed an experimental model with a *d*-tubocurarine infusion stabilized to produce a 90% depression of single twitch height (100% or the control value being twitch height without any relaxation), and assessed the temporary decrease of this block after neostigmine or physostigmine as indicating the extent and duration of action of these agents. These studies indicate that neostigmine 1,8 mg/m² has an effective half-life (i.e. mean time to 50% return of previously depressed twitch height) of 57,2 ± 6,1 minutes in humans, and 30% residual neostigmine activity is still present at 76,4 ± 6,1 minutes. Comparative figures after neostigmine 1,2 mg/m² are 41,0 ± 4,4 minutes for 50% return, and 57,8 ± 4,8 minutes for 70% return of previously depressed twitch height. The customary intravenous dosage of neostigmine 2,5 mg would usually fall between 1,2 and 1,8 mg/m².

Cronelly *et al.*³ evaluated the pharmacokinetics of neostigmine 0,07 mg/kg (4,9 mg for a 70 kg patient) in patients with normal kidney function. Initial peak plasma values of 200 - 350 ng/ml were found. This fell to 15 - 30 ng/ml after 1 - 2 hours. Neostigmine could be detected up to 2 hours after administration, using a gas/liquid chromatography technique. The mean elimination half-life of neostigmine (t_{1/2}) was 79,8 ± 48,6 minutes, while Morris *et al.*⁴ reported the t_{1/2} to be 77 ±

47 minutes at the same dosage. The dosages used by Cronelly *et al.* and Morris *et al.* were somewhat larger than the maximum used by Miller *et al.*²

As in the case of other drugs (e.g. propranolol, fentanyl) which are concentrated at certain tissue sites blood levels of neostigmine are probably not directly related to pharmacological effect (acetylcholinesterase inhibition in this case). However, Miller *et al.*² also reported that after intravenous neostigmine 1,8 mg/m² the mean time to 50% return of twitch height depression (effective half-life) was 57,2 ± 6,1 minutes. If one takes into consideration dosage differences, the t_{1/2} and effective half-life seem to correlate. Cronelly *et al.* also found a significantly increased t_{1/2} for intravenous neostigmine in anephric patients (181 ± 54 minutes).

Conclusions

1. The duration of action of neostigmine depends upon the dosage administered.
2. Depending on dosage, 30% of neostigmine activity may still be present 1 hour or more after administration.
3. Depolarizing relaxants should not be used before 1 hour (or more, depending on neostigmine dosage) has elapsed since neostigmine reversal, unless facilities for postoperative ventilatory assistance are present. Depolarizers should be diluted and a test dose administered. In anephric patients, increased duration of action of neostigmine may be expected.
4. When physostigmine is used for reversal, a safe time would probably be 50 - 100% longer than with neostigmine, i.e. 90 - 120 minutes.
5. In an acute emergency requiring re-intubation immediately after neuromuscular reversal, suxamethonium is probably the drug of choice, though the dosage for effective relaxation would be difficult to predict. Dilution of the depolarizer and administration as outlined in this article would seem reasonable and logical.

REFERENCES

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