ANTAGONISM OF NEUROMUSCULAR BLOCK BY PHYSOSTIGMINE IN MAN

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SUMMARY
In 20 adult patients undergoing inguinal herniorrhaphy neuromuscular block was induced with tubocurarine 10 mg. In 10 patients, neostigmine 1–2 mg antagonized the block and restored the twitch response to its baseline value. Physostigmine, up to 4 mg, did not produce significant antagonism of the neuromuscular block.

Physostigmine, an anticholinesterase with a tertiary amine structure, can cross the blood-brain barrier and has been used clinically to antagonize the central anticholinergic syndrome produced by hyoscine and other related alkaloids (Duvoisin and Katz, 1968; Greene, 1971; Holzgrafe, Vondrell and Mintz, 1973; Smiler et al., 1973). The drug has been shown in experimental animals to antagonize non-depolarizing neuromuscular block (Frank and McIntyre, 1948; Wescoe and Riker, 1951). However, it has not been reported that physostigmine, in the doses recommended for the reversal of the central anticholinergic syndrome, can reverse neuromuscular block in man. This report presents data on the ability of physostigmine to antagonize neuromuscular blockade in man, and compares its action with that of neostigmine.

METHOD
Observations were made on a total of 20 healthy adult patients, in the weight range 60–70 kg undergoing inguinal herniorrhaphy under general anaesthesia. The patients were premedicated with pethidine 100 mg and atropine 0.6 mg injected i.m., 30 min before operation. Anaesthesia was induced with sodium thiopentone 250–350 mg and maintained with halothane 0.5–1% in a mixture of nitrous oxide in oxygen (3 : 2). Ventilation was controlled throughout the procedure and \( P_{A}CO_{2} \) was maintained in the range 3.33–4.66 kPa. Tubocurarine 10 mg was administered to produce neuromuscular blockade.

The ulnar nerve was stimulated supramaximally at the wrist using a Block-Aid monitor which delivers an electrical pulse of approximately 0.2 ms duration at 4-s intervals (Katz, 1965). The stimulus was delivered via a 25-gauge steel hypodermic needle which served as the subcutaneous electrode. The resultant adduction of the thumb was detected by a force displacement transducer FT-03 and recorded on a Grass polygraph with a paper speed of 0.5 mm s\(^{-1}\). When a steady twitch response was obtained, repeated doses of neostigmine 0.5 mg were injected to achieve antagonism (10 patients). The response was compared with that achieved with physostigmine in a group of 10 similar patients.

RESULTS
In the first group of 10 patients, neostigmine 1–2 mg antagonized the neuromuscular block produced by tubocurarine 10 mg (fig. 1). The twitch height was restored always to its baseline value and was associated with a sustained response to tetanic stimulation (30 s\(^{-1}\)).

In the second group of patients, physostigmine 2 mg did not produce any significant antagonism of the neuromuscular block. An increase in the dose of physostigmine up to 4–8 mg was required to initiate antagonism. However, such antagonism was only partial, as demonstrated by incomplete restoration to the baseline twitch response or the presence of tetanic fade or both (fig. 2).

DISCUSSION
This report confirms previous experimental investigations which showed that physostigmine is less potent than neostigmine as an antidote to non-depolarizing neuromuscular block (Frank and McIntyre, 1948). The effects of physostigmine at the neuromuscular junction are considered to be secondary to a pure anti-acetylcholinesterase activity, whereas neostigmine can act both directly by a cholinomimetic mechanism and indirectly by its anticholinesterase activity (Wescoe and Riker, 1951; Koelle, 1970). Neostigmine is about 50 times as potent as...
Physostigmine in increasing the endplate potential and prolonging its time to half decay (Wescoe and Riker, 1951).

The pharmacological effects of an anticholinesterase agent depend in part on its lipid solubility. In general, a quaternary ammonium compound such as neostigmine does not penetrate cell membranes readily; hence it is excluded by the blood–brain barrier from exerting significant action on the central nervous system, and acts selectively on the neuromuscular junction of skeletal muscles. In contrast, a lipid-soluble tertiary amine compound such as physostigmine can readily cross the blood–brain barrier and act predominantly on the central nervous system (Koelle, 1970).

The present report shows that physostigmine does not adequately antagonize neuromuscular block in doses of up to 4 mg, which are recommended commonly for the antagonism of the central anticholinergic syndrome. Centrally, physostigmine not only inhibits brain cholinesterase, but can cause also direct excitation of neuronal activity, independent of the response to acetylcholine. The role of acetylcholine in neuromuscular transmission is entirely nicotinic, while cholinergic transmission in the brain is both muscarinic and nicotinic (Bradley, 1968). Therefore, it is not surprising to find that physostigmine has mechanisms which vary according to the site of action.

REFERENCES
ANTAGONISME DU BLOCAGE NEUROMUSCULAIRE PAR LA PHYSOSTIGMINE CHEZ L'HOMME

Resumen

Sobre 20 pacientes adultos sometidos a herniainguinal se indujo bloqueo neuromuscular con 10 mg de tubocurarina. En 10 pacientes, la neostigmina 1-2 mg resultó antagonica al bloqueo y devolvió la respuesta por sacudida muscular a su valor normal. La fisostigmina, hasta 4 mg, no produjo un antagonismo significativo del bloqueo neuromuscular.