NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE

Sir,—I read with great interest the recent paper of Payne, Hughes and Al Azawi (1980) on neuromuscular blockade by neostigmine.

Hardegg (1952) found that small doses of prostigmine blocked cholinesterase activity, while large doses of prostigmine occupied the acetylcholine receptors directly. In this way a neuromuscular blockade may be established as described by Payne and co-workers. Gallamine possibly dislodges prostigmine in part from the receptor site and facilitates the reappearance of acetylcholine at the receptor.

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Sir,—Dr Gebert presents an interesting hypothesis to explain our observations, but the work to which he refers (Hardegg, 1952) is concerned primarily with in vitro studies of the inhibition of erythrocyte cholinesterase by neostigmine and offers no experimental evidence to support the suggestion that large doses of neostigmine occupy the cholinergic end-plate receptors directly and so cause block.

First, it must be emphasized that we did not use large doses of neostigmine in our experiments to obtain neuromuscular block; doses of the order of 30–35 μg kg⁻¹ were sufficient. Second, the block obtained was antagonized by gallamine and enhanced by succinylcholine and must therefore be classified as depolarizing in nature.

The experimental evidence which has recently been reviewed in depth by Hobbiger (1976) is consistent with the view that inhibition of acetylcholinesterase by neostigmine largely accounts for the action of the drug and the simplest explanation is that neostigmine produces an acetylcholine-induced depolarization block by preventing the destruction of the transmitter at the motor end-plate. Certainly, there can be little doubt that this inhibition is responsible for both the twitch potentiation and for the tetanic fade after the administration of neostigmine demonstrated in our paper.

In the case of the single twitch response, while it is difficult to explain potentiation on the basis of receptor occupation by neostigmine, it is easily explained by the inhibition of acetylcholinesterase which allows acetylcholine access to nerve terminals from whence it triggers repetitive antidromic nerve action potentials and thus increased twitch tensions. This phenomenon, which was first demonstrated by Brown, Dale and Feldberg (1936), can be abolished by tubocurarine in doses that have no effect on normal twitch tension. The fact that, in our patients gallamine reduced the potentiated twitch response, confirms that the interaction is not specific to tubocurarine but probably can be demonstrated for all competitive blocking agents, and strengthens the argument in favour of a competitive action with acetylcholine.

Similarly, gallamine's ability to abolish tetanic fade and to restore normal tetanic wave forms during neuromuscular block by neostigmine reflects the antagonism between competitive and depolarizing neuromuscular blocking agents first highlighted by Paton and Zaimis in 1952, but previously implied by the work of Briscoe (1938), who showed that neostigmine could produce block in muscles rapidly tetanized and that tubocurarine in subparalytic doses could restore normal transmission.

Thus, available evidence supports the view that neuromuscular block induced by neostigmine is a result of the inhibition of acetylcholinesterase by the drug and of the consequent accumulation of acetylcholine at the neuromuscular junction.

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