A New Look at an Old Drug

EDROPHONIUM (Tensilon®), for a long time, has been thought to be too short-acting to be an acceptable antagonist of nondepolarizing neuromuscular blockades such as those produced by pancuronium or d-tubocurarine. Although Katz¹ concluded that edrophonium was not as effective as neostigmine in antagonizing profound neuromuscular blockades (i.e., those producing 75–100% depression of twitch tension), he did observe that even small doses (10 mg/70 kg) of edrophonium produced a small increase in twitch tension that did not abate. Twelve years later, Bevan² administered 2, 10, or 50 mg/70 kg iv of edrophonium to antagonize a pancuronium-induced neuromuscular blockade. Although only the 50 mg/70 kg dose completely antagonized the blockade, there was no evidence of a short duration of action (i.e., <60 min) with even the smaller doses. Kopman³ confirmed the efficacy of 0.5 mg/kg of edrophonium, although its antagonistic effects were unpredictable when only three or fewer twitches of the train-of-four were visible. Under similar circumstances, this unpredictability is also sometimes the case with neo- stigmine.

Since the Bevan² and Kopman³ publications, several other investigators have confirmed the efficacy of larger doses (i.e., 0.5–1.0 mg/kg) of edrophonium in antagonizing a nondepolarizing neuromuscular blockade. Its sustained antagonism is not surprising, since the pharmacokinetics of edrophonium and neostigmine were found later to be similar.⁴ Yet, the conclusion that the sustained duration of antagonism can be explained by the pharmacokinetics of edrophonium assumes a direct relationship between blood concentration of antagonist and magnitude and duration of antagonism, a relationship that has not been determined. A review by Cronnelly and Morris⁵ discussed the possibility that such a direct relationship between the concentration of antagonist in the blood and its effect may not exist.

Based on the limited number of patients studied, edrophonium appears to be as effective as either neostigmine or pyridostigmine in antagonizing a nondepolarizing neuromuscular blockade. Edrophonium also has two advantages. It has a short onset time (the time from administration of an antagonist to its peak effect), 0.8–2.0 min, compared with 7–11 min for neostigmine and 12–16 min for pyridostigmine.⁶ We believe an antagonist with a rapid onset of action is preferable, although its real impact on anesthetic practice has not been and probably is impossible to ascertain. The second advantage is that edrophonium requires about half as much atropine to block adverse cardiac muscarinic effects as does neostigmine.⁷ The assumption is that an antagonist that requires less atropine would be associated with fewer cardiac arrhythmias, although that conclusion has yet to be confirmed.

In this issue of Anesthesiology, Azar et al.⁷ establish that the selection of atropine or glycopyrrolate may depend on which antagonist is chosen. Obviously, the goal is to match the vagolytic effects of atropine or glycopyrrolate with the cardiac muscarinic effects of edrophonium and neostigmine. To have little or no change in heart rate requires giving the rapid-acting edrophonium and atropine together and the slower-acting neostigmine and glycopyrrolate together. Mixing edrophonium and glycopyrrolate initially produces bradycardia, whereas mixing neostigmine and atropine initially produces tachycardia. Whether these two mixtures are associated with a greater incidence of serious cardiac arrhythmias has not been determined. Thus, the clinical importance of studies on mixing antagonists and vagolytic drugs is difficult to ascertain.

Despite the apparent advantages, do we have enough information to confidently recommend edrophonium over neostigmine or pyridostigmine? Edrophonium only has been evaluated during anesthesia with halothane, intravenous drugs (e.g., narcotics) and nitrous oxide, or enfurane.⁷ Would dose-response, in terms of antagonism and interactions with vagolytic drugs, be different during isoflurane anesthesia? Also, edrophonium has a different mechanism of action than does neostigmine or pyridostigmine. Because edrophonium does not contain a carbamate group, its binding to the acetylcholinesterase enzyme is transient and easily reversed. Carbachylation of the esteric site by both neostigmine and pyridostigmine produces longer-lasting inhibition.⁸ Direct stimulation of the end-plate region has not been found to contribute to the anticholinergic action of edrophonium as it has for neostigmine.⁹ Therefore, edrophonium seems to have a predominantly presynaptic effect in comparison to neostigmine.

Because edrophonium has a different mechanism of action, would it behave as neostigmine and pyridostigmine during respiratory acidosis, electrolyte imbalance, administration of antibiotics, and other conditions? In other words, would all the studies that have been done with neostigmine and pyridostigmine need to be re-

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References

peated with edrophonium? In many cases, it probably would be intellectually unsatisfying and economically inappropriate simply to repeat all of these studies with edrophonium. Although less is known about edrophonium than neostigmine or pyridostigmine, its shorter onset and lower atropine requirement probably justify a preference for edrophonium over neostigmine or pyridostigmine as a routine antagonist. However, only when edrophonium has been used for thousands of patients will its proper position in regard to neostigmine and pyridostigmine be established.

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References

7. Azar I, Pham AN, Kambelkar DJ, Lear E: The heart rate following edrophonium-atropine and edrophonium-glycopyrrolate mixtures. ANESTHESIOLOGY 59:600–600, 1983