Is it always necessary to antagonize residual neuromuscular block?  
Do children differ from adults?

Use of an anticholinesterase at the end of surgery, to antagonize residual neuromuscular block induced by a non-depolarizing drug, is commonplace; it is easy to forget that such drugs were not always given routinely. When the clinical use of “Intocostrin” (a biologically standardized extract of curare) was first described in 25 patients by Griffith and Johnson in 1942, it was only recommended that an ampoule of the antidote, prostigmine, be readily available; there was no mention of administering the antagonist. Indeed, it is difficult to determine how anticholinesterases came into regular use. Neostigmine was noted only to be given “seldomly” by Prescott and colleagues in 1946, in doses of up to 5 mg, even though these workers were using tubocurarine 0.4 mg kg\(^{-1}\) for abdominal surgery. Undoubtedly, failure to use an anticholinesterase was a factor in the morbidity associated with the use of small doses of non-depolarizing neuromuscular blocking drugs in patients breathing spontaneously, and a reason why such techniques fell into disrepute in the early 1950s. Unfounded fears of neostigmine causing cardiac arrest were probably a reason for its omission. With the increasing use of larger doses of tubocurarine or pancuronium and controlled ventilation many, although not all, clinicians began to administer neostigmine 5 mg to adults. Large doses of anticholinesterase were used in children at this time: neostigmine 0.08 mg kg\(^{-1}\) was given to antagonize tubocurarine in neonates, who were thought to need an even higher dose than adults to obtain reliable recovery.

With the advent of the intermediate-acting non-depolarizing agents, atracurium and vecuronium, the need for such high doses of anticholinesterase was questioned. Clinicians soon realized that recovery from these agents was more rapid than with tubocurarine or pancuronium. The greater clearance of the newer drugs from plasma, and hence a more rapid decrease in relaxant concentration at the postsynaptic nicotinic receptor allowed, on some occasions, for the omission of an anticholinesterase. This has some benefits; nausea and vomiting may be less common in patients who are not given neostigmine after the use of a non-depolarizing drug. Any detrimental effect of neostigmine on a newly created gut anastomosis can also be avoided.

But careful monitoring of neuromuscular block is always necessary if anticholinesterases are not used. It is well recognized that even the clinicians most experienced in using monitoring techniques cannot detect decrement of the train-of-four twitch response by visual or tactile means, when the fourth twitch of the train has recovered to more than 40% of the first. It is essential therefore for all anaesthetists to quantify the train-of-four ratio if they are considering not using an anticholinesterase. Double burst stimulation, which consists of two or three bursts of 50 Hz tetanus, 750 ms apart, is thought to be more useful in detecting fade by visual or tactile means than the train-of-four response, although the differences are marginal. In addition, it is now thought that 80% recovery of the train-of-four ratio T4/T1 (and not 70% as first described\(^{15}\)), is a more reliable indicator of adequate recovery if electromyographic monitoring is used. This degree of spontaneous recovery may take much longer than is appreciated, even with atracurium or vecuronium. For example, the average time to spontaneous recovery of T1/T0 to 95% after atracurium 0.5 mg kg\(^{-1}\) is 68 min. But it is probable that with atracurium and vecuronium, neostigmine 2.5 mg in adults is an unnecessarily large dose to antagonize residual block, if greater than 20% recovery of T1/T0 has already occurred. Doses of neostigmine 1.25 mg are almost as effective. Even neostigmine 0.625 mg accelerates recovery after atracurium, although not after vecuronium.

The introduction of mivacurium, which is metabolized by plasma cholinesterase, again raised the question of whether or not it was always essential to antagonize residual block. Neostigmine, although not edrophonium, was known to inhibit plasma cholinesterase activity, and it was therefore postulated that neostigmine may potentiate mivacurium-induced neuromuscular block. There has been little evidence of such an effect, although neostigmine would only seem to speed recovery from mivacurium-induced block by a few minutes. The mean time for spontaneous recovery of T1/T0 from 25 to 75% (the recovery index) after a constant infusion of mivacurium is 7.7 min; if neostigmine 35 \(\mu\)g kg\(^{-1}\) is administered at 20% recovery of T1/T0, the recovery index is only reduced to 4.7 min. However, a few minutes add up to a long time if 10 laparoscopies are performed on a half-day list!

Plasma cholinesterase activity is greater in children than in adults and this is thought to explain the more rapid spontaneous recovery from mivacurium-induced neuromuscular block in the young. Whether mivacurium is given as a single bolus dose or by constant infusion in children, the benefit of using an anticholinesterase to speed recovery is questionable (if neuromuscular monitoring is being used), and edrophonium is a more appropriate agent than neostigmine to antagonize any residual block.

The longer-acting, non-depolarizing agents which are cleared more slowly from plasma have, of necessity, been antagonized routinely. But in children, Fisher and colleagues demonstrated that the dose–response curve for neostigmine, although not edrophonium, used to antagonize residual block from tubocurarine, was shifted to the left of that in adults, for the first time disputing the belief that larger doses of anticholinesterase were needed in the younger age group. As the distribution volumes and distribution half-lives of neostigmine and edrophonium are similar in all age groups, these differences
cannot be explained easily by a pharmacokinetic mechanism. It was postulated that local differences at the neuromuscular junction in children, such as the number of nicotinic receptors, amount of acetylcholine reserve or acetylcholinesterase activity, may be the causes of the lower dose requirements for anticholinesterases in paediatric patients. In addition, a more rapid circulation time in children speeds both delivery of anticholinesterase to the neuromuscular junction, hastening onset of effect, and also increases its rate of removal, shortening the duration of action. There is evidence, however, that it is the more rapid removal of the relaxant from the neuromuscular junction that is responsible for the more rapid recovery from block in children. Antagonism of neuromuscular block induced by pancuronium or doxacurium may be achieved with relatively smaller doses of neostigmine or edrophonium in children than in adults. Recovery rates from both blockers were similar in this study but in children, only half the weight-related dose of neostigmine or edrophonium used in adults was needed to produce the same effect. In an older study of recovery from pancuronium-induced neuromuscular block in children and adults, recovery of T1/T0 was found to be faster after large doses of edrophonium (1.43 mg kg⁻¹) than after a large dose of neostigmine (0.071 mg kg⁻¹) in all ages of children. Whichever anticholinesterase was used, recovery was more rapid in children than in adults.

In this issue, recovery from rocuronium-induced neuromuscular block is reported in children and in adults during isoflurane anaesthesia, using varying doses of neostigmine. Small doses of neostigmine after rocuronium 0.6 mg kg⁻¹ have a more marked effect in children aged 2–10 yr; for example, 5 μg kg⁻¹ produced as rapid a recovery of T4/T1 to 0.7 in children as neostigmine 50 μg kg⁻¹ in adults. These findings are impressive and, if substantiated, could alter paediatric anaesthetic practice significantly. Unlike mivacurium, spontaneous recovery in children and adults after rocuronium was at least twice as long as that induced by neostigmine 50 μg kg⁻¹. In children aged 1–5 yr during halothane anaesthesia, spontaneous recovery of T4/T1 to 0.75 after rocuronium 0.6 mg kg⁻¹ had previously been shown to occur in a mean time of 41.9 min, which is a shorter time than in adults. Of note is the wide range of recovery of T4/T1 to 0.75 (26.5–57.7 min). Such wide variation with the aminosteroid neuromuscular blocking agents is an indication for always using at least a small dose of anticholinesterase when these drugs are administered. It has been suggested, in an interim report, that recovery from rocuronium-induced neuromuscular block is slower in young children aged 1–4 yr than in older children aged 5–10 yr during halothane anaesthesia. Neostigmine administered at 25% recovery of T1/T0 again halved the recovery index (25–75% T1/T0) in both age groups. Further work is necessary on the pharmacokinetics and pharmacodynamics of rocuronium in children of all ages.

Nevertheless, it is becoming clear that, after administering the newer neuromuscular blocking agents, anaesthetists should again question if they are using too much neostigmine. If neuromuscular block is being monitored, and recovery is established (e.g. all four twitches of the train-of-four response are present), neostigmine 2.5 mg may be unnecessary in an adult who has received atracurium or mivacurium. Neostigmine 1.25 mg may be preferable. Decreasing the dose of the anticholinesterase may reduce its side effects. In children, smaller doses of anticholinesterase are necessary, even after using the aminosteroid neuromuscular blocking drugs, and especially with mivacurium, when they may not be needed at all!

**References**


