DO WE NEED MORE MUSCLE RELAXANTS?

In 1975 Savarese and Kitz [1] suggested that three new types of neuromuscular blocking drug were required. All should be non-depolarizing agents capable of antagonism and all should be free from cardiovascular side effects in therapeutic doses. The first type would replace suxamethonium, the second was to have a duration of action shorter than the competitive agents available at that time, and the third a longer action to replace pancuronium and tubocurarine. Since then two drugs, atracurium and vecuronium, have been introduced and have gained wide acceptance. It seems that we are about to be offered a further selection. Do we need the drugs on offer and do we still need further developments?

Atracurium and vecuronium were developed and marketed as drugs of intermediate durations of action. They were tested thoroughly in animal preparations to ensure that the doses necessary to show vagolytic, sympathomimetic or ganglion blocking actions were well in excess of those needed to produce neuromuscular blockade. They exhibit remarkably similar durations of action in equipotent doses and these durations are less than those possessed by the competitive agents hitherto available. Atracurium achieves this by having the, so far unique, property of Hofmann degradation whereby it degrades spontaneously when warmed to body temperature and placed at physiological pH. The fact that one of the end products is laudanosine, which is a central nervous system excitant in high doses does not appear to be clinically important even with prolonged use in intensive care patients in renal failure [2]. The absence of significant prolongation of action in renal or liver disease is a significant advantage [3, 4]. One disadvantage may be the dose-related release of histamine seen on occasion, although this and the associated haemodynamic response may be attenuated simply by slowing the speed of injection [5, 6]. In contrast, the short duration of action of vecuronium appears to result from rapid uptake by the liver, with elimination mainly in the bile but also by the kidney [7]. Some prolongation of the action of vecuronium may be seen with renal failure, with obstructive jaundice and with cirrhosis, but the extent is usually much less than is seen with conventional doses of pancuronium in healthy patients [8]. One additional problem is seen with both drugs. Neither shows vagolytic actions nor has sympathomimetic properties. Thus when they are used with opioids, with volatile agents such as halothane or when anaesthesia is insufficiently deep to prevent vagal responses to traction of viscera, there is a likelihood of bradycardia which may be severe enough to present as sinus arrest. The virtues of the drugs, however, have led to their wide acceptance for operations of intermediate duration.

In the past decade, there has also been a much better understanding of pharmacokinetics and pharmacodynamics. Both atracurium and vecuronium were marketed as being “non-cumulative”, which appeared to imply that when increments were given at a constant level of block, each increment produced a constant duration of block; but each drug was usually given as an initial large bolus and increments became necessary only to replace drug being lost by elimination. Thus “non-cumulation” could be expected and may be seen if the traditional agents such as tubocurarine and pancuronium are studied in the same way. Nevertheless, the idea of non-cumulation led to the use of both drugs by infusion which may lead to relatively easy maintenance of a constant level of block with easy antagonism when the operation has been completed [9]. By using either incremental bolus techniques or by using infusions, both drugs can be used satisfactorily for long operations. In effect they can be used as the Savarese-Kitz type III drugs. Atracurium seems effective and safe in those few patients who need paralysis in intensive care; it is not yet clear if vecuronium is equally effective and shows a rapid recovery.

What new drugs are on offer? On the West and East sides of the Atlantic there is some progress with developments of the benzylisoquinoliniums and the steroids, respectively. Two long acting drugs are available which appear devoid of cardiovascular side effects. Doxacurium (BW A938U) [10] and pipecuronium [11] are under-
going clinical trials in a number of centres. Their pharmacodynamic properties resemble those of pancuronium and they are probably also excreted largely by the kidney. Presumably, conditions which diminish glomerular filtration delay elimination, but they fit the bill should a replacement for pancuronium be needed. The absence of cardiovascular side effects may allow bradycardia to develop as a result of the vagotonic effect of certain anaesthetic agents and surgical stimuli. Their prolonged actions may also pose problems in antagonism of blockade, and anaesthetists will have to decide if they wish to use a single injection of the newer drugs compared with the ease of repeated bolus injections or infusions of atracurium or vecuronium. As for all prolonged operations, the use of a nerve stimulator will aid their safe administration.

There is one new drug with an action significantly shorter than that of atracurium or vecuronium. Mivacurium [12, 13] is another benzylisoquinolinium compound but, unlike atracurium, it is thought to undergo active hydrolysis by cholinesterase in addition to metabolism by hepatic microsomal enzyme systems. Its plasma clearance is faster than that of atracurium and with equipotent doses its action is 33–50% that of atracurium or approximately twice that of suxamethonium. Further, the recovery rate seems to be almost independent of the initial dose, and recovery times upon discontinuation of infusions have not differed significantly from times after single bolus doses. Its action is antagonized by neostigmine and it seems a better drug to use for those operations too long for a single dose of suxamethonium and too short for an intubating dose of atracurium or vecuronium. The temporary problem of the weak and floppy patient in the recovery room following attempted antagonism of drugs of intermediate duration of action after, say, 10–15 min, may be resolved but, as with more effective drugs, it possesses a disadvantage: its potential to release histamine seems to be equivalent to that of atracurium.

However, we still seem no nearer to replacing suxamethonium. Its unique triad of producing complete paralysis within 1 min of injection for a relatively short period of time implies that we shall continue to use it, although perhaps more sparingly than before. When there is an urgent need to facilitate tracheal intubation, to break laryngospasm and perhaps for short procedures such as electroconvulsive therapy, there is no equivalent substitute. It does, of course, have significant dangers: it can trigger malignant hyperpyrexia and it may produce life-threatening anaphylactoid reactions. It may lead to dangerous hyperkalaemia in the recently injured, in the burnt and in patients with upper and lower motor neurone lesions. It may not paralyse all patients, it provokes increases in intraocular pressure and it produces muscle pains. Can we identify why it remains so useful? Why do the other neuromuscular blocking agents not act so quickly [14], so well and for so short a time? There seem to be two features. First, we accept that there is a large margin of safety at the neuromuscular junction; the competitive blockers have to block all the spare receptors and most of the remaining 20–30% to produce complete block. In contrast, being a depolarizing drug, suxamethonium may need to produce depolarization only via the 20–30% to make the junction insensitive. Thus it may not need as high a concentration gradient to produce the effect. Second, because it has such a short half-life (of the order of 2–3 min at most in the normal patient) it can be given in a huge overdose, thus increasing the concentration gradient driving the drug towards the junction. The short half-life is associated with a very rapid decrease in concentration and, hence, rapid elimination. It remains to be seen if it is possible to produce a competitive blocker with a similar short half-life, but the signs are encouraging with the development of mivacurium.

To return to the question posed at the head of this editorial: “Do we need more muscle relaxants?” The answer is “yes”. One reason is that, as with most drugs containing quaternary nitrogen groups, anaphylactoid reactions occur to muscle relaxants and alternatives are needed. The introduction of new drugs always stimulates a critical examination of current practice and that is also an advantage. It is an open question if we need the long-acting replacements for pancuronium and tubocurarine, and this may be answered perhaps when we have more details of the variability in response to doxacurium and pipecuronium and an understanding of what factors predict prolonged responses. As described in this issue [15], mivacurium appears to be useful as a “short–intermediate” drug which may have a role in procedures such as those seen commonly in day-case centres. We still await the replacement for suxamethonium.

R.P.F. Scott and J. Norman
REFERENCES