British Journal of Anaesthesia 1996; **76**: 481–483

EDITORIAL II

Rocuronium: the newest aminosteroid neuromuscular blocking drug

Yet another non-depolarizing neuromuscular blocking drug may seem, especially to the older generation of anaesthetists, unnecessary. This is not so. We require a non-depolarizing agent with a rapid onset of action, in common with suxamethonium, but with a clinical duration of 10–12 min. Such an agent would not have the side effects associated with depolarizing drugs (e.g. hyperkalaemia, increased intraocular pressure, muscle pains) and ideally, its disposal would be independent of organ function.

It has perhaps been forgotten that when atracurium and vecuronium became available in 1982, both agents were found to have a shorter onset of action than the pre-existing non-depolarizing drugs. Maximum block after atracurium 0.5 mg kg^{-1} was achieved within 2.0 min, and after vecuronium 0.1 mg kg^{-1}, within 3 min [1]. These onset times were shorter than after tubocurarine 0.6 mg kg^{-1} at nearly 4.0 min [1], but were still longer than after suxamethonium 1.0 mg kg^{-1}. The depolarizing agent could be relied upon to produce maximum block within 1 min and, of the utmost importance, there was little variation in effect between individuals: the SD of that response was only 12 s [2].

In 1994, a new drug became available which narrowed this gap between the onset of action of suxamethonium and the non-depolarizing neuromuscular blocking drugs. Rocuronium has a similar structure to those of pancuronium and vecuronium (fig. 1). In common with vecuronium, rocuronium is a monoquaternary aminosteroid, but it is much less potent, with an ED_{95} (the dose required to produce 95% depression of the twitch response) of 0.3 mg kg^{-1} [3]. This lack of potency is thought to be an important factor in determining onset of neuromuscular block [4]. Whichever neuromuscular blocking drug is used, nearly all of the molecules at the neuromuscular junction are bound to the postsynaptic nicotinic receptor. The majority of these receptors must be occupied to produce neuromuscular block [5]; thus the number of molecules of a neuromuscular blocking drug which must enter the neuromuscular junction to produce a given degree of block is constant. But within a series of compounds, a less potent drug is given in a higher dose; a larger number of molecules are available to diffuse into the neuromuscular junction than the smaller number of molecules of a potent drug. A rapid onset of action is more likely to be achieved with a less potent agent.

Onset of block

Vecuronium has an ED_{95} of 0.056 mg kg^{-1} [6] and pancuronium an ED_{95} of 0.064 mg kg^{-1} [6]. It would therefore be expected that rocuronium, with an ED_{95} of 0.3 mg kg^{-1}, should have a more rapid onset of action than the older aminosteroids. Early clinical reports confirmed this. Rocuronium 0.6 mg kg^{-1} ($2 \times ED_{95}$) was found to have an onset of action of 60–90 s at the adductor pollicis muscle [7, 8]. The rate of onset is affected by anaesthetic technique: if the neuromuscular blocker is given immediately after the induction agent, then the onset time is a few seconds longer than in a research study, when steady-state anaesthesia has already been achieved with a volatile agent. At this dose, the block produced by rocuronium was not quite as predictable as suxamethonium: the range of effect was greater [9]. If the dose is doubled to 1.2 mg kg^{-1}, intubating conditions very similar to those produced by suxamethonium 1.0 mg kg^{-1} can be achieved reliably [9], but this dose of rocuronium ($4 \times ED_{95}$) has a duration comparable with that of pancuronium 0.1 mg kg^{-1}. Even with a small dose of rocuronium (0.45 mg kg^{-1}), a mean time to maximum effect of 72 s during halothane anaesthesia has been reported, although with an SD of almost 20 s [10].

As with other non-depolarizing neuromuscular blocking drugs, the laryngeal adductor muscles are more resistant to rocuronium than the adductor pollicis muscle (where neuromuscular block is often mentioned). After rocuronium 0.8 mg kg^{-1}, the peak effect in the laryngeal muscles is later, more variable and less profound than after suxamethonium 1.0 mg kg^{-1} [11]. The diaphragm is also more resistant to rocuronium than the adductor pollicis: an intubating dose of rocuronium 0.6 mg kg^{-1} has an effect at the diaphragm comparable with 0.5 mg kg^{-1} in the adductor pollicis [12]. Complete neuromuscu-

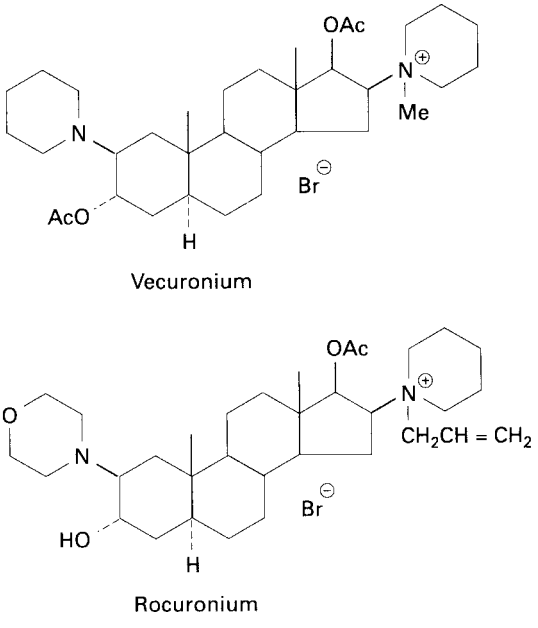

Figure 1 The monoquaternary aminosteroid, vecuronium, has an acetyl (AcO) group at the 3-carbon position. Deacetylation of vecuronium in the liver produces a 3-hydroxy metabolite which has approximately 50% of the neuromuscular blocking potency of vecuronium [23]. Rocuronium has a hydroxyl group at the 3-carbon position; unlike vecuronium, it will not undergo de-acetylation to produce a 3-OH metabolite with neuromuscular blocking activity.

lar block of the adductor pollicis does not imply that the laryngeal muscles and diaphragm are also completely paralysed.

If it is desirable to achieve a rapid onset of neuromuscular block and suxamethonium is contraindicated, for example in an emergency procedure in a patient with hyperkalaemia, or a patient with a penetrating eye injury, then rocuronium, in a dose of at least $2 \times ED_{95}$ (0.6 mg kg^{-1}), has a distinct advantage over other non-depolarizing neuromuscular blocking drugs. It is also preferable to a small "priming" dose of any other non-depolarizing neuromuscular blocking drug, before a paralysing dose, in an attempt to shorten the time to onset of maximum block [13]; there is no risk of curarization in a conscious patient.

If difficult intubation is anticipated, speed of onset of action is not of the utmost importance: profound block is required, from which rapid recovery can be obtained, if all attempts at intubation fail. In such cases, suxamethonium is still the ideal agent to use, because rocuronium is not a short-acting drug.

Recovery from block

Ten percent recovery of the first twitch of the train-of-four response (T1/T0) after rocuronium 0.45 mg kg^{-1} occurs in a mean time of 27 min during halothane anaesthesia [10]. During isoflurane anaesthesia, 10 % recovery of T1/T0 after rocuronium 0.6 mg kg^{-1} occurs in 34 min and 25 % recovery in 42 min [14]. After vecuronium 0.1 mg kg^{-1} in patients receiving neuroleptanaesthesia, 10 % recovery also occurs in a mean time of 27 min [1], and 25 % recovery in 44 min [15]. As with other aminosteroid neuromuscular blocking drugs, potentiation of rocuronium is greater during enflurane or isoflurane anaesthesia than during neuroleptanaesthesia [16], and neostigmine is more effective than edrophonium in antagonizing fade of the train-of-four response at the end of surgery [17].

Thus rocuronium does not have a short duration of action. Moreover, recovery from neuromuscular block occurs during drug redistribution, but the elimination half-life of rocuronium of 86 min [10] is longer than that for vecuronium (53 min) [18].

Renal failure patients

Animal studies have suggested that rocuronium is metabolized in the liver and excreted in bile; in cats, less than 10 % of a bolus dose was detected in urine in 24 h [19]. In humans, there is evidence that renal excretion may be greater: 30 % in 24 h in one study [20]. The use of rocuronium in patients with renal dysfunction has been reported; the results are conflicting. In a study of rocuronium 0.6 mg kg^{-1} in patients undergoing renal transplantation, onset and recovery times were similar to those of healthy patients [21]. Plasma clearance was similar in both groups, but volume of distribution at steady state was larger in renal patients (264 *vs* 207 ml kg^{-1} in healthy patients). This was thought to explain the longer elimination half-life of rocuronium in renal patients: 97 min compared with 71 min in healthy patients. Cooper and colleagues found longer mean recovery times after rocuronium 0.6 mg kg^{-1} in renal patients undergoing creation of an arteriovenous fistula, than in healthy patients, but this difference was not significant [22]. It is unlikely that rocuronium would produce such a reliable and predictable effect as atracurium in renal failure patients. For example, 25 % of T1/T0 after rocuronium 0.6 mg kg^{-1} in renal patients varies from 35 to 115 min; in healthy patients the range is 32–60 min [22].

Unlike vecuronium [23], the metabolites of rocuronium do not have neuromuscular blocking activity [24] (fig. 1). Rocuronium may not have the unpredictable effects of vecuronium if used for prolonged infusion in critically ill patients undergoing intensive therapy: pharmacokinetic studies of rocuronium and its metabolites in such patients are needed.

Cirrhotic patients

The limited evidence on the effect of rocuronium in patients with hepatic cirrhosis is also conflicting [25, 26]. Rocuronium 0.6 mg kg^{-1} has been shown to have a more variable and prolonged effect in this disease state. In one of the two reported studies [25], a reduction in clearance was demonstrated in cirrhotic patients, but this was not statistically significant. In a larger study however, there was more convincing evidence of reduced clearance and prolonged recovery after rocuronium 0.6 mg kg^{-1} in cirrhotic patients [J. M. Hunter, personal communication].

Cardiovascular effects

Atracurium and vecuronium were developed in part to overcome the cardiovascular effects of the older non-depolarizing agents (even though anaesthetists often used these effects to advantage, e.g. hypotension produced by tubocurarine when it was desired to reduce arterial pressure or the sympathomimetic effect of pancuronium in hypovolaemic patients). These drugs are free of such direct cardiovascular effects, but this allows other agents used during anaesthesia to have an unmitigated action, for example the bradycardia produced by opioid analgesics or halothane. In ophthalmic or gynaecological procedures, reflex bradycardia is often detected if atracurium or vecuronium are used. In some, although not all, studies in which rocuronium was given, there was evidence of a slight vagolytic effect [27, 28]. This was not as marked as with pancuronium, but clinicians will realize that they are dealing with a different agent from vecuronium in this respect. Indeed, this feature of rocuronium may be attractive, especially for use in healthy patients during procedures where vagal stimulation commonly occurs, for example cholecystectomy. As with other aminosteroid neuromuscular blocking drugs, there is no evidence of histamine release after the use of rocuronium [28].

Thus rocuronium may be a useful adjunct for clinicians in specific areas of their practice. The

onset of block is more rapid than with any other non-depolarizing neuromuscular blocking drug, but rocuronium has a duration of action which is at least as long as vecuronium. It may prove useful during that now rare event—general anaesthesia for Caesarean section [29]. But rocuronium is still not ideal: will Org 9487 one day fulfil the anaesthetist's desire for a rapid onset, rapid offset, non-depolarizing neuromuscular blocking drug [30]? This aminosteroid, which is undergoing clinical trials, is even less potent than rocuronium (ED_{90} 1.15 mg kg^{-1}). In addition to a rapid onset, it may be possible to antagonize the action of Org 9487 within a few minutes of administration. Will Org 9487 therefore become a replacement for suxamethonium? Read this journal for further developments in the field of neuromuscular pharmacology!

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