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''I would have everie man write what he knowes and no more.''—Montaigne

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Editorial

The doughnut and the hole: a new pharmacological concept for anaesthetists

It is time for anaesthetists to revisit a long acknowledged but little considered concept in clinical pharmacology. In our daily practice, we regularly think about the law of mass action, about reversible reactions and about diffusion gradients. We accept that passive diffusion along concentration gradients is a common cause of the pharmacological effects we utilize in every anaesthetic. Thus it is easy to conceive of recovery from neuromuscular block induced by the depolarizing agent, succinylcholine, occurring as the concentration of the drug reduces in the plasma following metabolism by plasma cholinesterase. The drug moves passively from the higher concentration at the postsynaptic nicotinic receptor back in to the plasma and recovery occurs. We also accept that if a further bolus dose of such a drug is given, neuromuscular block recurs: the balance of concentration of the drug would be shifted in the opposite direction.

From our undergraduate pharmacology days, we understand the concept of the 'lock-and-key' effect of enzymatic reactions. The endogenous compound or a drug and its receptor need to be in close proximity for interaction to occur, but in some circumstances an enzyme must also be present for the reaction to be completed. The classic example in anaesthesia is the presence of the enzyme, acetylcholinesterase, in the synaptic cleft at the neuromuscular junction. In normal circumstances, the neurotransmitter acetylcholine interacts with the α subunits of the postsynaptic nicotinic receptor, but its effect is rapidly terminated by the enzyme which breaks down acetylcholine within milliseconds. Again, this reaction is concentration dependent: an alteration in the concentration of the neurotransmitter or of the enzyme will affect the onset or termination of neurotransmission.

But in our practice it has been unusual, indeed rare, to use irreversible drug interactions on a regular basis. We all recall, in the distant past, being taught about *chelation* of lead in poisoned patients by oral administration of desferrioxime, but how often have we practised this technique? Once or twice, perhaps. There are other such reactions used in the treatment of drug poisoning, such as dimercaprol to chelate mercury and gold. Chelation of copper with penicillamine is also used in treating patients with Wilson's disease (hepatolenticular degeneration). But we would suggest that anaesthetists have little experience in using chelating agents.

Cyclic oligosaccharides

But now for something completely different! Pharmaceutical chemists have been aware for some time that a group of chemical substances known as *oligosaccharides* have the capacity to *chelate* or *encapsulate* certain endogenous and exogenous compounds. As the name suggests, oligosaccharides are low molecular weight sugars often of ring-like structure. One group of cyclic oligosaccharides is known as the *cyclodextrins*. They were discovered in the nineteenth century as crystalline by-products of starch degradation by bacteria. Cyclodextrins consist of six (α), seven (β) or eight (γ) glucose units linked into a ring-like structure. Their molecular weights are 973, 1135 and 1297 respectively. Such cyclodextrins have been used for some time as vehicles for topical drug administration.[1] They act as solubilizing agents for highly insoluble drugs. They are used as formulations for steroidal hormones and in targeted drug delivery systems for cancer chemotherapy. There has been a study on the use of a β cyclodextrin as a solvent for propofol, in an attempt to avoid the painful effects of administration of propofol in a lipid solvent.[2] Cyclodextrins have also been used to formulate a spinal preparation of bupivacaine, and for intranasal administration of midazolam.[1]

Do we need a new neuromuscular antagonist?

The outstanding challenge in neuromuscular pharmacology has been the design of a rapid onset, rapid offset relaxant which could be used for rapid sequence intubation. Ideally, reversal or recovery from such a drug would be so rapid that if intubation failed and the 'cannot intubate, cannot

ventilate' scenario arose, the life of a pre-oxygenated patient would not be at risk: recovery from block could be very rapidly achieved. Thus far, such ideal properties have been impossible to attain, but it is well recognized that of all the non-depolarizing neuromuscular blocking drugs available, rocuronium has the most rapid onset of action.[3] Nevertheless, this is a long-acting drug,[3] and reversal of its residual block with an anticholinesterase such as neostigmine can only be achieved when recovery is established: for instance, after 40 min when the second twitch (T2) of the train-of-four (TOF) response has become detectable (at least 20% recovery T_1).[3] In addition, although we use neostigmine every day, we do recognize its limitations. The most important is that it should only be given when recovery from block has been established and even then it takes at least 7 min to have its maximum effect. The muscarinic side-effects of an anticholinesterase can also be disadvantageous: nausea and vomiting may be potentiated in a patient with such a history; increased bowel motility may have an adverse effect on a (weak) gut anastomosis; cardiac arrhythmias may be worsened; and bronchospasm can occur.

Chelation (or encapsulation)

Now a γ cyclodextrin has been designed to encapsulate the aminosteroid non-depolarizing neuromuscular blocking agents. Org 25969, to be known as *sugammadex*, is a γ cyclodextrin designed to chelate or encapsulate rocuronium.[4] All available non-depolarizing neuromuscular blocking agents are quaternary ammonium compounds with at least one charged nitrogen atom $[N^+(CH_3)_3]$. γ Cyclodextrins have a lipophilic centre but a hydrophilic outer core, attributable to negatively charged ions on their surface. These negatively charged ions on the surface of sugammadex attract the positive charges of the quaternary ammonium relaxant, drawing the drug in to the central core of the cyclodextrin.[4] The binding of the guest molecule into the host cyclodextrin occurs because of van der Waal's forces and hydrophobic and electrostatic interactions. The interaction between rocuronium and sugammadex is particularly tight and long-lasting. The structure of the cyclodextrin is such that all four hydrophobic rings of the steroidal relaxant fit tightly within the concentric doughnut forming an inclusion complex. This has been confirmed by calorimetry and X-ray crystallography. Several other γ cyclodextrins have been investigated in animals as antagonists of rocuronium-induced block, but none are as efficacious as Org 25969.[5] Such a reaction occurs in the plasma—not at the neuromuscular junction—and the concentration of *free* rocuronium in the plasma has been shown in animal and human studies to decrease rapidly after sugammadex administration.[6 7] This is accompanied by a marked increase in total plasma rocuronium because of the amount of relaxant which has been encapsulated. The falling free concentration of plasma rocuronium causes the passive diffusion of the drug away from the postsynaptic nicotinic receptor into the plasma, in a way to which we are well used. The interesting difference is that the encapsulated complex is now freely filtered by the glomerulus into the urine.[6 7] The plasma clearance of the complex is the same as the glomerular filtration rate (120 ml min^{-1}). No dissociation of this tightly knit complex occurs in the plasma, however low the free concentration of rocuronium should decrease. This is in contrast to an enzymatic reaction: there is no reversibility about chelation. The key is tightly locked, bolted. The volume of distribution of rocuronium is *decreased* by the administration of sugammadex until it approaches that of the reversal agent: can you think of another example in anaesthetic practice of the pharmacokinetics of a drug changing so rapidly because of the administration of another? We cannot.

Dynamics of sugammadex (Org 25969)

Chelation occurs so rapidly that full recovery from neuromuscular block induced by rocuronium 1.2 mg kg^{-1} followed 5 min later by sugammadex 8.0 mg kg^{-1}, can be achieved within 3 min.[8] Allowing for the thorough mixing of a bolus dose of a drug in the circulation, which must take at least 45 s, this is very rapid indeed. It would be impossible to achieve recovery with an anticholinesterase so soon after administration of a non-depolarizing drug. It has been demonstrated repeatedly in humans and in animals that such rapid recovery can be obtained in the presence of profound neuromuscular block induced by varying doses of rocuronium.[6 7 9 10] With profound block, however, these larger doses of sugammadex are essential (4.0–8.0 mg kg^{-1}). Ten volunteers given rocuronium 0.6 mg kg^{-1} under general anaesthesia for intubation were reversed 3 min later with varying doses of Org 25969 or placebo. After Org 25969 8.0 mg kg^{-1}, the TOF ratio returned to 0.9 (when extubation can be safely effected) in 1 min.[7] After a lower dose of Org 25969 (2.0 mg kg^{-1}), recovery from profound block took longer (13 min), such that it would be of limited clinical benefit. In contrast, when recovery from block is established, a smaller dose of sugammadex is required. Shields and colleagues[11] showed that recovery of the TOF ratio to 0.9 after rocuronium given for up to 2 h, can occur in 1 min 46 s after sugammadex 2.0 mg kg^{-1}, if it is not administered until T2 is detectable. The number of patients in each sub-group given a variable dose of sugammadex was small (4–6), but nevertheless these early clinical results are also encouraging. There has been no evidence yet from either animal or human studies of recurarization occurring after the administration of sugammadex, even when the drug is given in the presence of profound neuromuscular block.

Other aminosteroid agents do not interact as tightly with sugammadex, but animal and human studies suggest that if larger doses of the cyclodextrin (at least 4 mg kg^{-1}) are given when T2 has reappeared, vecuronium can be

adequately antagonized.[12] At this early stage, it does seem that sugammadex would need to be given in even larger doses to be efficacious in reversing pancuronium.[4 13] In contrast, and importantly, sugammadex does not antagonize residual block induced by the benzylisoquinolinium relaxants such as atracurium and mivacurium.[14] This is predictable: the more bulky benzylisoquinolinium structures will not be incorporated into the small cavity of the cyclodextrin (the hole). The pharmacodynamics of the rocuronium–sugammadex complex have recently been discussed in detail in an editorial by Kopman.[13]

Side-effects

As cyclodextrins are water-soluble, sugar molecules, which do not possess intrinsic biological activity, they should be well tolerated in humans. Allergic reactions to dextrose compounds would be unusual, but there are concerns that cyclodextrins could encapsulate other steroidal drugs and indeed endogenous steroids such as glucocorticoids, sex hormones and aldosterone. Animal work has suggested that sugammadex can encapsulate cortisone and hydrocortisone as well as atropine and verapamil, but its affinity for these drugs is up to 700-fold less than for rocuronium.[4] It is uncertain whether sugammadex will encapsulate oestrogens or hormone contraceptives; more work is required in humans in this respect. There is some *in vitro* work suggesting that sugammadex may interact with remifentanil, although not other narcotic analgesics.[4] As sugammadex has no direct effect on cholinergic transmission, no muscarinic side-effects should occur, and the use of an antimuscarinic with it is unnecessary.

Other possible side-effects include reports, from human volunteer studies, of prolongation of the QT interval of the ECG.[7] This effect is recognized with several anaesthetic agents including sevoflurane and morphine: its clinical significance is uncertain. If you monitor the ECG in detail during anaesthesia, you would probably see this phenomenon quite frequently. Again, only time will tell if the effect has any clinical significance. There have also been occasional reports of transient hypotension after larger doses of sugammadex.[9 15]

You may be concerned that the rocuronium/sugammadex complex is excreted mainly in the urine,[6 7] with only limited enterohepatic circulation and biliary excretion. Indeed, the urinary excretion of free rocuronium increases after sugammadex administration.[6 7] What happens to this complex in the patient with no or minimal renal function? In contrast to the use of neuromuscular blocking drugs, an antagonist is only given in a single dose (at least, usually). Recovery from the effect of an i.v. bolus dose of any drug occurs by redistribution, not elimination. This is thought to be the reason why the effect of this selective relaxant binding agent in patients with renal dysfunction is unaltered. Much work is still required, however, in this vulnerable patient group.

Side-effects from any new drug that becomes clinically available are not usually detected until several thousand patient exposures have occurred: remember the saga with rapacuronium.[16] Is there really no recurarization after sugammadex? Only time will tell. We would point out that most of the reported human studies have been carried out using total i.v. anaesthesia. Will the use of potent inhalational agents have any effect on recovery from block with sugammadex, as they do with neostigmine? We await the outcome of such studies.

The future

More than 700 human subjects have received sugammadex so far in clinical trials. The drug is due to be launched in the USA within the year and in Europe by 2008. What practical concerns are there for British anaesthetists with this new pharmacological concept? Many of us want to use the same antagonist to reverse residual block produced by any non-depolarizing neuromuscular blocking drug. It must not be forgotten, however, that in the USA and Australasia rocuronium is by far the most widely used non-depolarizing agent. You may well argue that the pharmaceutical industry is attempting to lure you into using a new compound and your scepticism would be pertinent. If you appreciate the benefits of a new antagonist, you may be tempted only to use the neuromuscular blocking agent it reverses. Certainly, once you have used this new selective relaxant binding agent, you will be impressed by its speed of action. Its variability of effect still needs to be ascertained in large numbers of patients, however, and we await the almost inevitable side-effects: no perfect drug exists. Nevertheless, we are on the threshold of another exciting development in neuromuscular pharmacology.[17]

J. M. Hunter[*†]
E. A. Flockton

University Department of Anaesthesia
Clinical Science
Duncan Building
Daulby Street
Liverpool L69 3GA
UK

[*]*E-mail: bja@liv.ac.uk*

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