Rajinder K Mirakhur

MD PhD FRCA

R K Mirakhur worked with Professor John Dundee and Dr RS Clarke (Reader in Anaesthetics) in Belfast. He was appointed senior lecturer in 1990 and to a personal chair in 1996[i]. He is well known for his work on drugs that work at the neuromuscular junction. The neuromuscular junction is the point at which the South American 'arrow poison' curare works, and changed anaesthetic practice for ever. Curare competes with acetyl choline (ACh) at the junction between the motor nerve and the muscle. ACh facilitates the electrical impulse from the nerve to the muscle that causes a muscle to contract – curare blocks this and causes paralysis which makes surgery easier and means that anaesthesia can be 'lighter'.

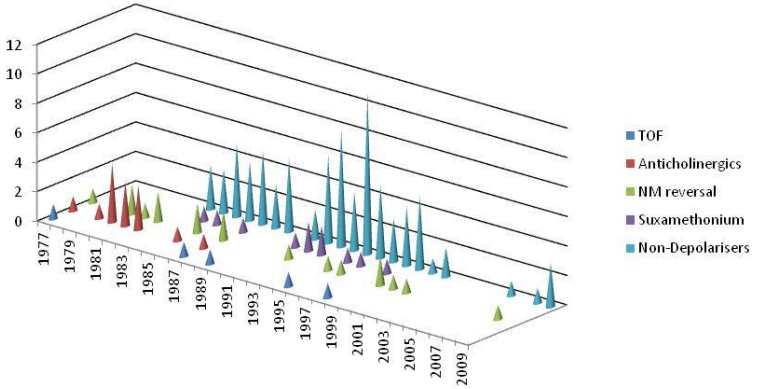
The following drugs cause paralysis – suxamethonium (depolariser) and the rest (non-depolarisers) pancuronium, vecuronium, atracurium, doxacurium, mivacurium, pipecuronium, rapacuronium and rocuronium.

The following are antidotes to non-depolarisers – neostigmine and edrophonium (the author has never seen this used in clinical practice, nor pyridostigmine), and now sugammadex. Atropine and glycopyrrolate prevent bradycardia and salivation secondary to neostigmine.

Mirakhur studied all these drugs, and more, and the technique used for studying the degree of neuromuscular blockade is the electrical stimulation of the nerve and the assessment of either the electrical effect on the muscle (EMG) or the physical movement of the muscle. The most commonly used patterns of electrical stimulation are the 'so-called' Train-Of-Four (TOF) or a tetanic stimulus. The former is a series of four electrical shocks which

[i] J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916

produces different patterns of muscle contraction, the greater the degree of paralysis the larger the difference between the 1st and the 4th muscle twitch, the T1-T4 ratio. A tetanic stimulus is a continuous series of electrical shock that cause a continuous muscle contraction.



This represents the number of papers published each year for the five different categories. 1987, 1993 and 1995 were the busiest years with 10, 10 and 14 paper respectively – an extraordinary rate of publication.

Monitoring the Neuromuscular Junction

Mirakhur's first publication was in 1972; his first publication about neuromuscular blockade was in 1977, and the first specifically on the TOF ten years later in 1987. We will address the monitoring of the neuro-muscular junction first as it will create a foundation for the understanding of the other work.

The 'Train-of-Four' (TOF)

"*Four consecutive stimuli are delivered along the path of a nerve, and the four responses of the muscle (T1, T2, T3 and T4) is measured in order to evaluate stimuli that are blocked versus those that are delivered*" [ii]

The first in 1987 [74] was to determine the TOF value that might indicate that another dose of muscle relaxant was necessary. The TOF

[ii] http://medical-dictionary.thefreedictionary.com/train-of-four

responses were measured during recovery of neuromuscular block (paralysis) from atracurium, vecuronium, pancuronium and tubocurarine in order to quantify the height of T1 at which T2, T3 and T4 reappear. The 4th response (T4) appeared at approximately 30% height of T1 (previously thought to occur at 25%). It was recommended that the appearance of T3 (at about 25% of T1) be used as the trigger for a further dose of muscle relaxant.

In 1989 [90] fade in the TOF responses during onset of neuromuscular block was studied following administration of atracurium, vecuronium, pancuronium and tubocurarine. TOF ratios (T1:T4, fade) were measured at heights of T1 of 75, 50 and 25%. Fade increased as the height of T1 decreased; maximum fade at T1 of 25%. Vecuronium showed the least fade and pancuronium, atracurium and tubocurarine showed increasing fade. I'm unsure of the significance of these results.

Again in 1989, the fade in response to tetanic stimulation was studied [89]. Patients received atracurium, vecuronium, pancuronium and tubocurarine and tetanic fade was measured either at maximum block or at 10% recovery depending on the dose given. They stated that "*If fade in response to tetanic stimulation represents a prejunctional effect ... that neuromuscular blocking drugs cannot be differentiated with respect to their relative prejunctional effects by measurement of tetanic fade...*"

This was followed six years later by "*Nondepolarizing neuro-muscular blocking drugs and train-of-four fade*" [144]. Again, the aim was to assess differences in prejunctional effects of different relaxants but this time by measuring the TOF fade. It was concluded that the relative prejunctional effects of the relaxants were similar.

In the same year they assessed a new TOF monitor [141]. The TOF-Guard (it incorporated an accelerometer) was compared to a standard mechanomyographic (Myograph 2000). When the data were analysed using the Bland and Altman technique the 95% limits of agreement were not so close. They recommend that results from the TOF-Guard and the Myograph 2000 should not be considered equivalent but that the TOF-Guard was an improvement on tactile evaluation of the TOF.

Once again, in 1998, fade associated with TOF stimulation was examined [167]. The fade, which was thought to be due to a prejunctional

effect[iii], was assessed after doses of cisatracurium, atracurium, vecuronium, mivacurium or rocuronium. The TOF fade (during onset and offset of the block) was greater with a low dose of cisatracurium compared with all other relaxants. Cisatracurium, a stereoisomer of atracurium, had a slower onset of action than all the others but the duration of action was similar.

In 2001 Mirakhur wrote an editorial in the European Journal of Anaesthesiology on "*Current developments in anaesthesia and neuromuscular transmission*" [190].

We will now examine some of the muscle relaxants, many occur in various combinations in the same study.

Curare was first prepared in 1832
Suxamethonium was discovered in 1906 but the neuromuscular blocking properties were not described until 1949
Pancuronium was synthesised in 1964
Vecuronium was synthesised in 1973
Atracurium was synthesised in 1974
Rocuronium was introduced to clinical practice in 1994

The 1970s and 80s were a great time for NMB investigations.

Suxamethonium
The aspects of this depolarising agent that were investigated were its duration of action, the muscle pain that followed its use and associated biochemical changes, the pretreatments aimed at reducing this side effect, the management of associated bradycardia and the speed of onset compared with other agents. The latter is described in the following section on nondepolarisers.

Bradycardia occurs subsequent to administering a second dose and the effect is minimised by the use of antimuscarinic agents. In 1979 they wished to determine the efficacy of a new agent, glycopyrrolate, and compared it with the standard drug atropine, and so they studied patients who received intermittent doses of suxamethonium [16]. There were 28 patients in each group. "*Although no statistically significant differences were seen, clinically,*

[iii] Bowman WC. Anesthesia and Analgesia 1980; 59: 935–43.

glycopyrrolate seems to afford better protection against the cardiac changes resulting from intermittently administered suxamethonium." Considering the lack of statistical significance the following statement of efficacy seems unsupported.

Another early paper, in 1984, [49] was a report of the investigation of how long suxamethonium's effect lasted in children, and the plasma cholinesterase activity. There was no difference in cholinesterase activity between children and adults but the apnoea was of shorter duration in children; it was suggested that this might have been due to their larger volume of extracellular fluid.

Suxamethonium is well recognised clinically by the muscle fasciculations that occur before paralysis, by the cellular release of creatine kinase (CK) and by the subsequent muscle pains, myalgia. Myalgia, although an unwanted, unpleasant side effect, was never considered a contraindication to the use of suxamethonium in clinical situations where its use was considered necessary. However a variety of measures were tried to reduce its severity: In 1983 pretreatment with vecuronium and neuromuscular blocking agents [42], in 1985 pretreatment with benzodiazepines [52] and in 1992/93 there were two papers on the biochemical changes associated with myalgia with various pretreatments [113, 119].

Pretreatment with nondepolarisers [42]: Patients were assessed for muscle pain on the 1st and 2nd postoperative days. Vecuronium, gallamine, tubocurarine or pancuronium were given one or two minutes before the suxamethonium. The incidence of pain was halved with pretreatment (from 40% to 20%).

Pretreatment with benzodiazepines: Several studies investigated these phenomena. Diazepam and midazolam failed to reduce the myalgia but tubocurarine was effective as a pretreatment; it virtually abolished fasciculation but it also reduced the intensity and duration of the neuromuscular block [52]. Changes in serum potassium, creatinine phosphokinase and aldolase were clinically insignificant..."..... *although 5 out of 47 showed an atypical rise in creatinine phosphokinase.*"

The release of creatine kinase was increased if suxamethonium and halothane were used together in chicks [100], this did not occur to a significant degree when the drugs were used individually. The release of CK was thought to be due to muscle damage, possibly by the involvement of phospholipases because it was prevented by chlorpromazine. In a clinical study [113] myalgia

was reduced by tubocurarine, chlorpromazine and alphatocopherol but only those who received tubocurarine and chlorpromazine had reduced CK efflux. As expected intubation conditions were not as good with the pretreatment with tubocurarine. A further study examined the effect of hypnotic induction agents [119], propofol or thiopentone. It was concluded that they had no effect on myalgia or CK release.

How did the pretreatments affect the neuromuscular blockade produced by suxamethonium [124]? Those pretreated with chlorpro-mazine, alpha-tocopherol or aspirin had no significant difference in time to maximum block or time to recovery of twitch response compared with those receiving no pretreatment. Those pretreated with d-tubocurarine took longer to achieve maximum block and the duration was shorter compared with those receiving no pretreatment. It was considered that chlorpromazine was the better drug in the prevention of the side effects of succinylcholine.

A relatively uncommon clinical scenario with suxamethonium is where it is necessary to re-intubate a patient after a non-depolarising agent has been 'reversed'[iv] with an anticholinesterase. The speed of onset of and duration of action of suxamethonium was assessed after the use of edrophonium or neostigmine (both anticholinesterases)[145]. Both the onset and duration were prolonged and plasma cholinesterase activity was reduced after neostigmine.

Non-depolarising muscle relaxants

Combinations:

Some of the earlier Mirakhur studies compared all three commonly used agents – pancuronium, vecuronium and atracurium [57, 66, 81, 86]. It was a great time for NMB investigations. Many other drugs were studied but few survived – rocuronium was a survivor. (*see below*)

Quickness of onset and duration of action of muscle relaxants are of clinical significance. In 1985, in a group of patients over 65 years of age, pancuronium, vecuronium and atracurium were assessed. The intubating conditions were similar but the time to complete block was shortest with vecuronium at 4.3 minutes, the differences were not significant. Atracurium and vecuronium, however, lasted a significantly shorter time, 35 vs. 99 minutes.

[iv] 'Reversed': a colloquial term for the administration of an antidote for the termination of the action of a non-depolarising muscle relaxant.

Other clinically significant factors were the effects on the cardio-vascular system. In 1986 the heart rate, rhythm and systolic, diastolic and mean arterial pressures were measured after giving atracurium, vecuronium or pancuronium in the presence of a standard anaesthetic. Pancuronium caused an increase in blood pressure and heart rate (and a junctional rhythm). Vecuronium caused a fall in diastolic blood pressure and some patients had signs of histamine release after atracurium.

To try and reduce the time from the patient going to sleep and the time to intubation the idea of a small 'starter' dose followed by a later dose was considered. In 1988 this was studied with the three agents. Ten percent of the total dose was given four minutes before the second dose. There were no significant differences between the single and divided dose groups.

Dose-response curves are a mainstay of pharmacokinetics and in 1989 were constructed for atracurium, vecuronium and pancuronium in another set of elderly patients. There appeared no significant differences between elderly and young adult subjects.

From the table below it can be seen that the main interests were vecuronium, atracurium and rocuronium with mivacurium a runner up.

	Panc	**Vec**	**Atrac**	**Cisa**	**Dox**	**Miv**	**Pip**	**Rap**	**Roc**
Panc	2	7	4	0	0	0	2	0	0
Vec		13	8	0	0	0	0	0	1
Atrac			8	2	0	1	0	0	0
Cisa				0	0	0	0	0	1
Dox					1	0	0	0	0
Miv						9	0	0	1
Pip							1	0	0
Rap								4	1
Roc									21

The comparison studies will be left for the reader to examine but some of the more interesting studies will be described.

Plasma cholinesterase [45]
Plasmacholinesterase (aka pseudocholinesterase) is produced in the liver and found in the plasma. Levels may be reduced in advanced liver disease but only a reduction to <25% of normal will result in significant prolongation of neuromuscular blockade with suxamethonium. Levels can be affected by various anaesthetic agents and so plasma cholinesterase levels were measured following pancuronium and vecuronium. Pancuronium produced a significant reduction in the enzyme levels but vecuronium was without any significant effect. Vecuronium was always considered a 'clean' drug.

Drug interactions: these are always important. The following were studied: doxapram, H2 receptor blockers, beta-blockers, calcium channel antagonists and anticonvulsants.

Doxapram is a respiratory stimulant and it may be used at the end of anaesthesia to improve ventilation and therefore increase the elimination rate of volatile agents without affecting analgesia. There was some evidence that it enhanced neuromuscular block and so the rates of spontaneous and neostigmine-induced recovery were studied; the time from 25% recovery of T1 to 75% (RI). It was significantly longer after vecuronium in the presence of doxapram but there was no significant difference after atracurium or when neostigmine was administered. This suggested that only if neo-stigmine reversal was incomplete, a prolonged recovery might result [105].

H_2 receptor blockers, cimetidine and ranitidine, are used to reduce gastric acid production. At the time there was "*conflicting evidence about the occurrence of interactions between H2-receptor blocking agents and neuromuscular blocking drugs.*" So a study of single oral doses of cimetidine or ranitidine on the neuromuscular blocking effects of vecuronium and atracurium was undertaken. With vecuronium the times following cimetidine were prolonged significantly but there were no significant differences in any of the variables following ranitidine pretreatment. Cimetidine pretreatment had no affect on atracurium [99].

Beta-blockers, calcium entry blocking drugs and anticonvulsants: The affects of these agents had been well studied on the neuromuscular junction and rocuronium at this time was a new drug and their effects with this agent needed to be assessed. Neuromuscular block was monitored during a fentanyl, propofol infusion and nitrous oxide anaesthetic. There were no differences in onset times. Apart from chronic therapy with anticonvulsant drugs, which

reduces the duration of action of rocuronium, there were no other significant changes [162].

Intra-ocular pressure: The effect on **intra-ocular pressure** was of importance as it is necessary to avoid excessive pressure if the globe is damaged or open during surgery. In all there were eight studies [64, 65, 79, 80, 84, 85, 91, 96].

The first, in 1985, was a comparison of the effects of Diprivan (propofol) and thiopentone. The next, in 1986. determined the effects of atracurium or succinylcholine during nitrous oxide-oxygen-fentanyl anaesthesia. Intra-ocular pressure was stable with atracurium but succinylcholine caused a significant increase. Thiopentone was associated with a decrease in pressure but it increased in both groups as a result of laryngoscopy and intubation [65].

In 1987 the effect of vecuronium was assessed during a normal induction of anaesthesia sequence (thiopentone + vecuronium) and during a rapid induction sequence (vecuronium + thiopentone). Vecuronium was associated with a decrease in intra-ocular pressure and even though tracheal intubation caused an increase it never exceeded pre-induction levels [80].

A year later a report was published in ***Anaesthesia*** where intra-ocular pressure was measured during induction of anaesthesia with propofol or thiopentone followed by vecuronium. The results were similar to previously [84] and in the same year in the ***BJA*** something similar again [85]. Post-intubation, intra-ocular pressure in the propofol group remained significantly less than the baseline value.

Infusions: Muscle relaxants are very suitable for use as infusions as their pharmacological effect is easily measured and therefore the dosage easily titrated.

In 1984 [50] it was shown that when vecuronium was given as a continuous intravenous infusion the dose required to maintain a steady state at 90% block was, on average, 0.083 mg kg^{-1} h^{-1} (5.8 mg h^{-1} for a 70kg patient). Although there were large variations recovery was quick when the infusion was stopped. Five years later prolonged infusions (15-68h) in an intensive care unit were studied [88]. Recovery on cessation of the infusions took almost half an hour. No adverse affects were noted. A similar study was reported in 1991, this time in a paediatric intensive care unit [97]. Eleven infants and children and

four neonates received an infusion to maintain a 90% block for between 9.5 and 179 hr. The mean doses were in the region of 0.1 $mg.kg^{-1}hr^{-1}$. The recovery times were in the region of 50 minutes. Again no adverse effects were noted.

Mivacurium and rocuronium were the subjects of subsequent infusion studies.

Thirty patients were infused with mivacurium during thiopentone, fentanyl and halothane anaesthesia [129]. Reversal was with either neostigmine or edrophonium, or spontaneous recovery was allowed. A significant negative correlation ($r = -0.81$, $p < 0.001$) was shown between time to recovery from the initial bolus dose.

In the same year rocuronium infusions were used [132]. Following a bolus dose of 0.45 mg kg^{-1} an infusion was adjusted manually to maintain T1 at 10%. Again neostigmine or edrophonium, or spontaneous recovery was allowed. Inter-patient dose requirements varied. Reversal with neostigmine and edrophonium was about four times quicker than spontaneous recovery which took about 36 minutes. Because of variable recovery rates neostigmine was considered a more reliable antagonist.

The final study was a pharmacokinetic study of rocuronium infusions [156]. The average rocuronium infusion rate for a steady state 90% block of T1 was about 0.5 mg kg^{-1} h^{-1}. Spontaneous recovery time was about 30 minutes. Blood samples collected over six hours post infusion were analysed for concentrations of rocuronium and metabolites using HPLC. The pharmacokinetic data "were not significantly different from previously published data for a single bolus dose of rocuronium".

Reversal of neuromuscular blockade

Reversal of neuromuscular blockade can be left to nature (spontaneous recovery) or can be stimulated by overcoming the existing competitive block between the neuromuscular blocking agent and acetyl choline (Ach). This is achieved by increasing the levels of ACh by decreasing its rate of breakdown by using an anticholinesterase. However an antidote is required for the antidote because anti-cholinesterases also have unwanted side effects: bradycardia and salivation. To oppose these effects atropine (old) and glycopyrrolate (relatively new, patented in 1960) are used. To complete the picture the newest, most expensive, and novel agent, sugammadex was also investigated.

The first four papers (1977-81) [10, 23, 24, 32] were comparative studies of atropine and glycopyrrolate. In the first a glycolpyrro-

late/neostigmine ratio of 0.2 mg /1.0 mg was thought safe and effective, heart rate was stable but the antisialogogue action of glycopyrrolate was superior. Arrhythmias were similar in both groups. The second paper was similar but they added another anticholinergic, antimuscarinic drug hyoscine. The third was a study in children (atropine vs. glycopyrrolate) and the fourth was a study where the effects were assessed if the neostigmine was given with, or after atropine and glycopyrrolate. If the drugs have different onset times then the overall effect could potentially be different. Given first, both anticholinergic agents produced an increase in heart rate which decreased after the administration of neostigmine. The bottom line was that anticholinergic drugs should be administered with neostigmine and that glycopyrrolate, 10 μg kg^{-1} produced a stable heart rate.

The second set of papers [37, 40] was about the effect of neostigmine and pyridostigmine on serum cholinesterase activity. Acetyl-cholinesterase is considered the target but there was evidence that they also inhibited serum cholinesterase (pseudocholinesterase). Serum cholinesterase activity was measured after reversal of pancuronium blockade and the enzyme activity was significantly depressed. The clinical importance is that a subsequent dose of suxamethonium could be prolonged; if a non-depolariser were to be given for further neuromuscular blockade an increased dose would be required. In 1986 [67] a similar study was done with edrophonium; this was after atracurium, there was no inhibition of enzyme activity. It was suggested that in previous studies the use of pancuronium may have been partially responsible for the depression of enzyme activity.

There were other comparative studies [56, 76, 77, 145]. However, one non-depolarising drug that is different to the others is mivacurium. It is metabolised by the action of plasma cholinesterase. In this study [160] it was given after the reversal, with neostigmine or edrophonium, of an atracurium induced block. As might be expected the action of mivacurium was prolonged by neostigmine but not by edrophonium.

We must now address the novel drug sugammadex [194, 198-200, 202, 204]. The action of this agent is akin to the way an antibody attaches itself to an antigen. The drug attaches itself to rocuronium (and less efficiently) to vecuronium and the pharmacological action is terminated, almost

immediately[v]. Prior to this agent the early reversal of a non-depolarising neuromuscular blocking drug was virtually impossible. Attempting to reverse the block early caused problems and increasing the dose of the anticholinergic can cause an increase in the neuromuscular block!

2006: [194] Sugammadex, Org 25969, a cyclodextrin, was studied to determine its efficacy. After a profound block with rocuronium various doses of sugammadex were given. The time to achieve a TOF ratio to 0.9 was recorded and there was a dose-related decrease. It was determined that the fastest time possible to get to a TOF ratio of 0.9 to be 1:35 minutes and that a dose of 2-4 mg kg^{-1}would be effective.

2008: [198] This study compared the reversal of rocuronium-induced neuromuscular block with sugammadex with that of neostigmine for reversal of cisatracurium. The reversal agent was administered when T2 appeared and it was shown that recovery to a TOF ratio of 0.9 was 4.7 times faster with sugammadex than with neostigmine. [The author would like to ask: Why not compare rocuronium reversal with neostigmine with rocuronium reversal with sugammadex?]

2009: [200] This was a review article. It described how the neuromuscular block of both rocuronium and vecuronium can be reversed by sugammadex; for a shallow block 2mg kg^{-1}, for a deep block 4mg kg^{-1}, for a really deep block (16 mg kg^{-1}). Using 1-1.2 mg kg^{-1} of rocuronium produces a rapid block which raised "*the possibility of using rocuronium as a replacement for suxamethonium*". Sugammadex was said to have an "*acceptable safety profile*".

[v] The author was fortunate in being the recipient of both the first box of rocuronium in New Zealand, and the first box of sugammadex. Sugammadex is, simultaneously, both an exciting and boring drug. It works extraordinarily well and has virtually no side effects (apart from a few drug interactions). The first time he used it the rapidity and completeness of recovery appeared almost miraculous. A reflection, perhaps, of 30 year's experience of slow and less than 100% recovery; the cognitive recovery of the patient also seemed enhanced (an impression and, of course, anecdotal).

2009: [202] This was a phase IIIA study to explore the efficacy and safety of sugammadex in infants, children, adolescents and adults. All was well, it rapidly, effectively and safely reversed rocuronium neuromuscular blockade in all patients.

2011: [204] Rescue reversal refers to the situation where a neuromuscular blocking drug has been and the airway cannot be secured. The quick return of spontaneous breathing is required. This letter pointed out some facts in previously reported studies including that by Hogg et al. Journal of Anaesthesia 2010; 105: 726–727P. Return of diaphragmatic movement was recorded about 40seconds after a 16 mg kg^{-1} dose of sugammadex. With pre-oxygenation this should maintain oxygen saturation It was pointed out in the letter that the storage place for the sugammadex should be widely known so that it should be available within one minute, and the dose should be known: 3 vials of 500 mg[vi].

Anticholinergics

There are 25 papers involving atropine, or glycopyrrolate or hyoscine [10-12, 14, 16, 20, 23-26, 28-33, 35, 38, 39, 43, 58-60, 78, 135]. Excluding those already mentioned which ones are of particular interest?

Hypersensitivity to atropine [11]

This is a 10 line letter – *"...We were interested in the case report of hypersensitivity to atropine by Giala and Tzovairi-Tsakona (1978). A safer and appropriate alternative to atropine is glycopyrronium."*

Gastric acidity and glycopyrrolate premedication [20]

This letter was making comment about a paper by Baraka et al (Anesth Analg 1977; 56:642- 645). They make the point that the doses of the two anticholinergics studied were not comparable. Their observations showed that 0.2 mg of glycopyrrolate and 1.0 mg of atropine were indistinguishable regarding the effects on pH of gastric contents. They also criticised the statistical tests used and the data presented They said that anticholinergic

[vi] At this time (2011) the cost of sugammadex in New Zealand was about 1$ / mg. This was not a cheap exercise.

agents reduced the opening pressure of the cardio-oesophageal sphincter and in addition they reduce the motility and "*perhaps*" delay gastric emptying. They believed that obstetric anaesthesia would be safer with cimetidine and metoclopramide. Glycopyrrolate they considered better than *"the dubious and unproven attribute of raising the pH of gastric contents."*

Atropine premedication and respiratory complications [29]

This was a letter in response to an article by Jones and Drummond[vii] who showed that atropine did not change the frequency of postoperative respiratory complications. Mirakhur and Clarke were questioning why atropine was used routinely for premedication when it had no obvious benefit [19, 21] and left the patient with a dry mouth. Routine anti-cholinergic medication has not been used in routine anaesthetic practice for several decades; coinciding with a move against intramuscular premedication.

Antiemetic effects [31, 135]

This [31]was also a letter but a very detailed one – a mini-paper! The message from this was that glycopyrrolate does not have an anti-emetic action and this was thought to be due to its inability to cross the blood-brain barrier.

This was revisited in 1995 [135]. Children having squint surgery, who are prone to vomiting, were studied to assess the effectiveness of anticholinergics as antiemetics. The incidence of the intra-operative oculocardiac reflex was also recorded. Glycopyrrolate and atropine reduced the incidence of the oculocardiac reflex by over 90%. There was no significant difference in emesis between the placebo group and the anticholinergics.

Now for the non- neuromuscular studies:

Propofol

Propofol was studied with regard to intraocular pressure [64, 79, 84, 85], propofol-opiate anaesthesia [126, 134, 158, 188, 193] and propofol and cellular function [138, 197]. The last two are of interest.

[vii] Jones GC and Drummond GB. Br J Anaesth. 1981;53:441

Delayed hypersensitivity reactions and T lymphocyte proliferation were studied. Thiopentone and propofol were given to volunteers as an infusion on two occasions. Skin antigen tests were carried out before and after administration. The results showed that the reactions were depressed but there was no effect on T lymphocyte proliferation [138].

The second study was about the protective effect of propofol on myocardial contractility during ischaemia. Rat ventricular cardiomyocytes were made ischaemic for two hours. Under normal conditions, propofol decreased the contraction of cardiomyocytes by approximately 37%. However, during ischemia, propofol was associated with responses where ischaemic values were equal to normal values. This showed that propofol can offset the effects of free radical compounds on cardiomyocytes undergoing oxidant stress and actually improve contractility [197].

Remifentanil

Remifentanil was studied with regard to cardiovascular effects [177, 180, 183], recovery from anaesthesia [184, 188] and case reports of three adrenalectomies [191].

Remifentanil can suppress the cardiovascular effect of laryngoscopy/intubation [177] and so its use for adrenalectomies seemed appropriate. There were no adverse events during resection of an adrenal cortical tumour but there was hypotension and bradycardia. It did not prevent increases in blood pressure or plasma catecholamine levels during excision of the two phaeochromocytoma, even with alpha and beta blockade [191].

The elderly

The elderly were also studied – seven related to neuromuscular blockade but another two were about pre- and post-anaesthesia oxygenation.

In brief - [98] It was decided that, in those over 65 years of age, at least two minutes preoxygenation was necessary to give the maximum apnoea time before oxygen saturation dropped to 93%.

[111] This study was in patients over 70 years of age having eye surgery. Oxygen saturation was recorded on the pre-operative night, immediately postoperative, within the first 60 minutes, and then on the first postoperative night. The percentage of time during which the patients had an oxygen saturation of less than 90% was less than 0.15%. There were no

differences between general and local anaesthesia for this minimally invasive surgery.

Laryngoscopes

Finally, a series of five studies about a new laryngoscope [123, 143, 147, 157, 192].

The first four are about the McCoy designed laryngoscope – McCoy is a co-author in each paper. The McCoy laryngoscope had a modified Macintosh blade; it had a hinged tip that was activated by a lever on the handle. It enhanced the ability to elevate the epiglottis and it was claimed to reduce the difficulty of larynx visualisation associated with an anterior larynx [123]. The second [143] was a technical paper on measuring the forces exerted at laryngoscopy which was then used to compare laryngoscopy with the Macintosh and McCoy blades [157]. The year before a comparison was also made by assessing the cardiovascular changes, at laryngoscopy, with the two blades.

The final one in the series [192] was a modification of the modification – an adjustable mirror was added to the blade. Using in-line neck stabilisation to simulate difficult intubation, the mirrored laryngoscope out performed both the McCoy and the Macintosh. It was concluded this new laryngoscope offered "*considerable advantages over the Macintosh and the McCoy laryngoscopes*"; McCoy was not involved in this study.

Mirakhur was the first author in 79 of these studies. He had many co-authors. A number were RS Clarke, involved in 32 publications, Elliott P 21, Gibson FM 21, McCoy EP 20, Maddineni VR 17, Lavery GG 16, McCarthy GJ 15, Cooper RA 13, Ferres CJ 10 and Reid J 10.

After 34 years studying neuromuscular blockade I think I might have become a bit jaded with train-of-four ratios. However, it all ended with sugammadex, a very interesting exciting and stimulating endgame.

References

1. Mirakhur, R.K., *Percutaneous anesthesia for endoscopy.* Archives of Surgery, 1972. **105**(3): p. 531.
2. Mirakhur, R.K., *Technique for difficult intubation.* British Journal of Anaesthesia, 1972. **44**(6): p. 632.
3. Dadve, A.V. and R.K. Mirakhur, *Ophthalmic hypersensitivity to anaesthetic vapours.* Anaesthesia, 1973. **28**(3): p. 338-9.
4. Mirakhur, R.K., *Correspondence: Simple and reliable method of inserting a nasogastric tube during anaesthesia.* British Journal of Anaesthesia, 1973. **45**(10): p. 1062.
5. Mirakhur, R.K. and A. Bandopadhyay, *Correspondence: An auditory guide to the location of the extradural space.* Anaesthesia, 1973. **28**(6): p. 707.
6. Mirakhur, R.K., *Airway obstruction with cuffed armoured tracheal tubes.* Canadian Anaesthetists' Society Journal, 1974. **21**(2): p. 251-3.
7. Mirakhur, R.K. and A.V. Badve, *Pregnancy and anaethetic practice in India.* Anaesthesia, 1975. **30**(1): p. 18-22.
8. Dundee, J.W., C.J. Jones, and R.K. Mirakhur, *The evaluation of the anticholinergic activity of glycopyrronium [proceedings].* British Journal of Clinical Pharmacology, 1977. **4**(3): p. 383P-384P.
9. Mirakhur, R.K., *Use of air in a continuous flow anaesthetic machine.* British Journal of Anaesthesia, 1977. **49**(5): p. 520.
10. Mirakhur, R.K., J.W. Dundee, and R.S. Clarke, *Glycopyrrolate-neostigmine mixture for antagonism of neuromuscular block: comparison with atropine-neostigmine mixture.* British Journal of Anaesthesia, 1977. **49**(8): p. 825-9.
11. Dundee, J.W. and R.K. Mirakhur, *Hypersensitivity to atropine.* British Journal of Anaesthesia, 1978. **50**(8): p. 866.
12. Mirakhur, R.K., *Comparative study of the effects of oral and i.m. atropine and hyoscine in volunteers.* British Journal of Anaesthesia, 1978. **50**(6): p. 591-8.
13. Mirakhur, R.K., et al., *Anticholinergic drugs in anaesthesia. A survey of their present position.* Anaesthesia, 1978. **33**(2): p. 133-8.
14. Mirakhur, R.K., et al., *Atropine and glycopyrronium premedication. A comparison of the effects on cardiac rate and rhythm during induction of anaesthesia.* Anaesthesia, 1978. **33**(10): p. 906-12.

15. Mirakhur, R.K., J.W. Dundee, and C.J. Jones, *Evaluation of the anticholinergic actions of glycopyrronium bromide.* British Journal of Clinical Pharmacology, 1978. **5**(1): p. 77-84.
16. Cozanitis, D.A., J.W. Dundee, and R.K. Mirakhur, *Atropine versus glycopyrrolate. A study using repeated doses of suxamethonium in man.* Acta Anaesthesiologica Belgica, 1979. **30 Suppl**: p. 151-7.
17. Mirakhur, R.K., *Anticholinergic drugs.* British Journal of Anaesthesia, 1979. **51**(7): p. 671-9.
18. Mirakhur, R.K., *Intravenous administration of glycopyrronium: effects on cardiac rate and rhythm.* Anaesthesia, 1979. **34**(5): p. 458-62.
19. Mirakhur, R.K. and J.W. Dundee, *Cardiovascular changes during induction of anaesthesia. Influence of three anticholinergic premedicants.* Annals of the Royal College of Surgeons of England, 1979. **61**(6): p. 463-9.
20. Mirakhur, R.K. and J.W. Dundee, *Gastric acidity and glycopyrrolate premedication.* Anesthesia & Analgesia, 1979. **58**(2): p. 157-9.
21. Mirakhur, R.K., J.W. Dundee, and J.D. Connolly, *Studies of drugs given before anaesthesia. XVII: anticholinergic premedicants.* British Journal of Anaesthesia, 1979. **51**(4): p. 339-45.
22. Mirakhur, R.K., J. Reid, and J. Elliott, *Volume and pH of gastric contents following anticholinergic premedication.* Anaesthesia, 1979. **34**(5): p. 453-7.
23. Bali, I.M. and R.K. Mirakhur, *Comparison of Glycopyrrolate, atropine and hyoscine in mixture with neostigmine for reversal of neuromuscular block following closed mitral valvotomy.* Acta Anaesthesiologica Scandinavica, 1980. **24**(4): p. 331-5.
24. Black, G.W., et al., *Reversal of non-depolarising neuromuscular block in children: a comparison of atropine and glycopyrrolate in a mixture with neostigmine.* Anaesthesia, 1980. **35**(9): p. 913-6.
25. Cozanitis, D.A., et al., *Evaluation of glycopyrrolate and atropine as adjuncts to reversal of non-depolarizing neuromuscular blocking agents in a "true-to-life" situation.* British Journal of Anaesthesia, 1980. **52**(1): p. 85-9.
26. Mirakhur, R.K. and J.W. Dundee, *Comparison of the effects of atropine and glycopyrrolate on various end-organs.* Journal of the Royal Society of Medicine, 1980. **73**(10): p. 727-30.

27. Mirakhur, R.K., J.W. Dundee, and J.D. Connolly, *Anticholinergic premedication.* British Journal of Anaesthesia, 1980. **52**(4): p. 467.
28. Mirakhur, R.K., et al., *Comparison of atropine and glycopyrrolate in a mixture with pyridostigmine for the antagonism of neuromuscular block.* British Journal of Anaesthesia, 1981. **53**(12): p. 1315-20.
29. Mirakhur, R.K. and R.S. Clarke, *Atropine premedication and respiratory complications.* British Journal of Anaesthesia, 1981. **53**(11): p. 1233.
30. Mirakhur, R.K. and J.W. Dundee, *Glycopyrrolate.* General Pharmacology, 1981. **12**(6): p. 423-7.
31. Mirakhur, R.K. and J.W. Dundee, *Lack of anti-emetic effect of glycopyrrolate.* Anaesthesia, 1981. **36**(8): p. 819-21.
32. Mirakhur, R.K., et al., *Reversal of neuromuscular blockade: dose determination studies with atropine and glycopyrrolate given before or in a mixture with neostigmine.* Anesthesia & Analgesia, 1981. **60**(8): p. 557-62.
33. Mirakhur, R.K., C.J. Jones, and J.W. Dundee, *Effects of intravenous administration of glycopyrrolate and atropine in anaesthetised patients.* Anaesthesia, 1981. **36**(3): p. 277-81.
34. Clarke, R.S. and R.K. Mirakhur, *Antagonism of neuromuscular block.* British Journal of Anaesthesia, 1982. **54**(7): p. 793-4.
35. Mirakhur, R.K., *Premedication with atropine or glycopyrrolate in children. Effects on heart rate and rhythm during induction and maintenance of anesthesia.* Anaesthesia, 1982. **37**(10): p. 1032-6.
36. Mirakhur, R.K., *Bradycardia with laryngeal spraying in children.* Acta Anaesthesiologica Scandinavica, 1982. **26**(2): p. 130-2.
37. Mirakhur, R.K., R.S. Clarke, and P.S. Collier, *Effects of neostigmine and pyridostigmine on serum cholinesterase activity.* Canadian Anaesthetists' Society Journal, 1982. **29**(3): p. 287.
38. Mirakhur, R.K. and C.J. Jones, *Atropine and glycopyrrolate: changes in cardiac rate and rhythm in conscious and anaesthetised children.* Anaesthesia & Intensive Care, 1982. **10**(4): p. 328-32.
39. Mirakhur, R.K., et al., *I.m. or i.v. atropine or glycopyrrolate for the prevention of oculocardiac reflex in children undergoing squint surgery.* British Journal of Anaesthesia, 1982. **54**(10): p. 1059-63.
40. Mirakhur, R.K., et al., *Effects of neostigmine and pyridostigmine on serum cholinesterase activity.* Canadian Anaesthetists' Society Journal, 1982. **29**(1): p. 55-8.

41. Ferres, C.J., P.M. Crean, and R.K. Mirakhur, *An evaluation of Org NC 45 (vecuronium) in paediatric anaesthesia.* Anaesthesia, 1983. **38**(10): p. 943-7.
42. Ferres, C.J., et al., *Pretreatment with vecuronium as a prophylactic against post-suxamethonium muscle pain. Comparison with other non-depolarizing neuromuscular blocking drugs.* British Journal of Anaesthesia, 1983. **55**(8): p. 735-41.
43. Mirakhur, R.K. and J.W. Dundee, *Glycopyrrolate: pharmacology and clinical use.* Anaesthesia, 1983. **38**(12): p. 1195-204.
44. Mirakhur, R.K., et al., *Clinical evaluation of Org NC 45.* British Journal of Anaesthesia, 1983. **55**(2): p. 119-24.
45. Mirakhur, R.K., C.J. Ferres, and T.D. Lavery, *Plasma cholinesterase levels following pancuronium and vecuronium.* Acta Anaesthesiologica Scandinavica, 1983. **27**(6): p. 451-3.
46. Mirakhur, R.K., et al., *Cutaneous reaction after atracurium.* Anaesthesia, 1983. **38**(8): p. 818-9.
47. Ferres, C.J., et al., *Dose-response studies with pancuronium, vecuronium and their combination.* British Journal of Clinical Pharmacology, 1984. **18**(6): p. 947-50.
48. Lavery, G.G. and R.K. Mirakhur, *Atracurium besylate in paediatric anaesthesia.* Anaesthesia, 1984. **39**(12): p. 1243-6.
49. Mirakhur, R.K., P. Elliott, and T.D. Lavery, *Plasma cholinesterase activity and the duration of suxamethonium apnoea in children.* Annals of the Royal College of Surgeons of England, 1984. **66**(1): p. 43-5.
50. Mirakhur, R.K. and C.J. Ferres, *Muscle relaxation with an infusion of vecuronium.* European Journal of Anaesthesiology, 1984. **1**(4): p. 353-9.
51. Mirakhur, R.K., et al., *Time course of muscle relaxation with a combination of pancuronium and tubocurarine.* Anesthesia & Analgesia, 1984. **63**(4): p. 437-40.
52. Chestnutt, W.N., et al., *Failure of two benzodiazepines to prevent suxamethonium-induced muscle pain.* Anaesthesia, 1985. **40**(3): p. 263-9.
53. Gibson, F.M., et al., *Comparison of cumulative and single bolus dose techniques for determining the potency of vecuronium.* British Journal of Anaesthesia, 1985. **57**(11): p. 1060-2.

54. Gibson, F.M., et al., *Potency of atracurium: a comparison of single dose and cumulative dose techniques.* Anesthesiology, 1985. **62**(5): p. 657-9.
55. Lavery, G.G., M.M. Boyle, and R.K. Mirakhur, *Probable histamine liberation with atracurium. A case report.* British Journal of Anaesthesia, 1985. **57**(8): p. 811-3.
56. Lavery, G.G., R.K. Mirakhur, and F.M. Gibson, *A comparison of edrophonium and neostigmine for the antagonism of atracurium-induced neuromuscular block.* Anesthesia & Analgesia, 1985. **64**(9): p. 867-70.
57. Lowry, K.G., et al., *Vecuronium and atracurium in the elderly: a clinical comparison with pancuronium.* Acta Anaesthesiologica Scandinavica, 1985. **29**(4): p. 405-8.
58. Mirakhur, R.K., *Antagonism of the muscarinic effects of edrophonium with atropine or glycopyrrolate. A comparative study.* British Journal of Anaesthesia, 1985. **57**(12): p. 1213-6.
59. Mirakhur, R.K., *Glycopyrrolate and human plasma cholinesterase.* Canadian Anaesthetists' Society Journal, 1985. **32**(6): p. 683-4.
60. Mirakhur, R.K., *Antagonism of neuromuscular block in the elderly. A comparison of atropine and glycopyrronium in a mixture with neostigmine.* Anaesthesia, 1985. **40**(3): p. 254-8.
61. Mirakhur, R.K., *Anaesthetic management of vitrectomy.* Annals of the Royal College of Surgeons of England, 1985. **67**(1): p. 34-6.
62. Mirakhur, R.K., F.M. Gibson, and C.J. Ferres, *Vecuronium and d-tubocurarine combination: potentiation of effect.* Anesthesia & Analgesia, 1985. **64**(7): p. 711-4.
63. Mirakhur, R.K., et al., *Atracurium in clinical anaesthesia: effect of dosage on onset, duration and conditions for tracheal intubation.* Anaesthesia, 1985. **40**(8): p. 801-5.
64. Mirakhur, R.K. and W.F. Shepherd, *Intraocular pressure changes with propofol ('Diprivan'): comparison with thiopentone.* Postgraduate Medical Journal, 1985. **61 Suppl 3**: p. 41-4.
65. Lavery, G.G., et al., *The effects of atracurium on intraocular pressure during steady state anaesthesia and rapid sequence induction: a comparison with succinylcholine.* Canadian Anaesthetists' Society Journal, 1986. **33**(4): p. 437-42.

66. Lavery, G.G., et al., *The effect of atracurium, vecuronium and pancuronium on heart rate and arterial pressure in normal individuals.* European Journal of Anaesthesiology, 1986. **3**(6): p. 459-67.
67. Mirakhur, R.K., *Edrophonium and plasma cholinesterase activity.* Canadian Anaesthetists' Society Journal, 1986. **33**(5): p. 588-90.
68. Mirakhur, R.K., et al., *Intubating conditions after vecuronium and atracurium given in divided doses (the priming technique).* Acta Anaesthesiologica Scandinavica, 1986. **30**(5): p. 347-50.
69. Mirakhur, R.K., W.F. Shepherd, and C.J. Jones, *Ventilation and the oculocardiac reflex. Prevention of oculocardiac reflex during surgery for squints: role of controlled ventilation and anticholinergic drugs.* Anaesthesia, 1986. **41**(8): p. 825-8.
70. Pandit, S.K., et al., *Time course of action of combinations of vecuronium and pancuronium.* Anaesthesia, 1986. **41**(2): p. 151-4.
71. Pandit, S.K., et al., *Premedication with cimetidine and metoclopramide. Effect on the risk factors of acid aspiration.* Anaesthesia, 1986. **41**(5): p. 486-92.
72. Brady, M.M., R.K. Mirakhur, and F.M. Gibson, *Influence of "priming" on the potency of non-depolarizing neuromuscular blocking agents.* British Journal of Anaesthesia, 1987. **59**(10): p. 1245-9.
73. Gibson, F.M. and R.K. Mirakhur, *Dose-response curves for pancuronium and tubocurarine: comparison of single and cumulative dose techniques.* European Journal of Anaesthesiology, 1987. **4**(2): p. 143-7.
74. Gibson, F.M., et al., *Quantification of train-of-four responses during recovery of block from non-depolarising muscle relaxants.* Acta Anaesthesiologica Scandinavica, 1987. **31**(7): p. 655-7.
75. Lavery, G.G., et al., *Does the choice of the neuromuscular blocking agent affect the cardiovascular response to intubation?* Acta Anaesthesiologica Scandinavica, 1987. **31**(3): p. 239-43.
76. Mirakhur, R.K., *Antagonism of pancuronium and tubocurarine blocks by edrophonium or neostigmine: a comparative study.* European Journal of Anaesthesiology, 1987. **4**(6): p. 411-9.
77. Mirakhur, R.K., F.M. Gibson, and G.G. Lavery, *Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine.* British Journal of Anaesthesia, 1987. **59**(4): p. 473-7.

78. Mirakhur, R.K. and C.J. Jones, *Plasma cholinesterase activity following administration of glycopyrrolate or atropine.* Canadian Journal of Anaesthesia, 1987. **34**(2): p. 219-20.
79. Mirakhur, R.K., W.F. Shepherd, and W.C. Darrah, *Propofol or thiopentone: effects on intraocular pressure associated with induction of anaesthesia and tracheal intubation (facilitated with suxamethonium).* British Journal of Anaesthesia, 1987. **59**(4): p. 431-6.
80. Mirakhur, R.K., et al., *The effects of vecuronium on intra-ocular pressure.* Anaesthesia, 1987. **42**(9): p. 944-9.
81. Brady, M.M., R.K. Mirakhur, and R.S. Clarke, *Administration of vecuronium, atracurium and pancuronium in divided doses: effect on onset and duration of action.* European Journal of Anaesthesiology, 1988. **5**(4): p. 243-9.
82. Mirakhur, R.K., *Anticholinergic drugs and anaesthesia.* Canadian Journal of Anaesthesia, 1988. **35**(5): p. 443-7.
83. Mirakhur, R.K., *Induction characteristics of propofol in children: comparison with thiopentone.* Anaesthesia, 1988. **43**(7): p. 593-8.
84. Mirakhur, R.K., et al., *Intra-ocular pressure changes during induction of anaesthesia and tracheal intubation. A comparison of thiopentone and propofol followed by vecuronium.* Anaesthesia, 1988. **43 Suppl**: p. 54-7.
85. Mirakhur, R.K., W.F. Shepherd, and P. Elliott, *Intraocular pressure changes during rapid sequence induction of anaesthesia: comparison of propofol and thiopentone in combination with vecuronium.* British Journal of Anaesthesia, 1988. **60**(4): p. 379-83.
86. Bell, P.F., R.K. Mirakhur, and R.S. Clarke, *Dose-response studies of atracurium, vecuronium and pancuronium in the elderly.* Anaesthesia, 1989. **44**(11): p. 925-7.
87. Bell, P.F., R.K. Mirakhur, and P. Elliott, *Onset and duration of clinical relaxation of atracurium and vecuronium in patients on chronic nifedipine therapy.* European Journal of Anaesthesiology, 1989. **6**(5): p. 343-6.
88. Darrah, W.C., J.R. Johnston, and R.K. Mirakhur, *Vecuronium infusions for prolonged muscle relaxation in the intensive care unit.* Critical Care Medicine, 1989. **17**(12): p. 1297-300.
89. Gibson, F.M. and R.K. Mirakhur, *Tetanic fade following administration of nondepolarizing neuromuscular blocking drugs.* Anesthesia & Analgesia, 1989. **68**(6): p. 759-62.

90. Gibson, F.M. and R.K. Mirakhur, *Train-of-four fade during onset of neuromuscular block with nondepolarising neuromuscular blocking agents.* Acta Anaesthesiologica Scandinavica, 1989. **33**(3): p. 204-6.
91. Mirakhur, R.K., *Intra-ocular pressure and rapid sequence induction of anaesthesia.* Anaesthesia, 1989. **44**(7): p. 611-2.
92. Stanley, J.C. and R.K. Mirakhur, *Comparative potency of pipecuronium bromide and pancuronium bromide.* British Journal of Anaesthesia, 1989. **63**(6): p. 754-5.
93. McCarthy, G.J., C. McLoughlin, and R.K. Mirakhur, *Neuromuscular blockade in von Recklinghausen's disease.* Anaesthesia, 1990. **45**(4): p. 340-1.
94. Mirakhur, R.K., *Drug usage by anaesthetists.* Anaesthesia, 1990. **45**(6): p. 500-1.
95. Mirakhur, R.K., *Side effects of atracurium.* British Journal of Anaesthesia, 1990. **64**(1): p. 124-5.
96. Mirakhur, R.K., et al., *Comparison of the effects of isoflurane and halothane on intraocular pressure.* Acta Anaesthesiologica Scandinavica, 1990. **34**(4): p. 282-5.
97. Fitzpatrick, K.T., et al., *Continuous vecuronium infusion for prolonged muscle relaxation in children.* Canadian Journal of Anaesthesia, 1991. **38**(2): p. 169-74.
98. McCarthy, G., et al., *A comparison of different pre-oxygenation techniques in the elderly.* Anaesthesia, 1991. **46**(10): p. 824-7.
99. McCarthy, G., et al., *Effect of H2-receptor antagonist pretreatment on vecuronium- and atracurium-induced neuromuscular block.* British Journal of Anaesthesia, 1991. **66**(6): p. 713-5.
100. McLoughlin, C., et al., *Pathogenesis of suxamethonium-induced muscle damage in the biventer cervicis muscle in the chick.* British Journal of Anaesthesia, 1991. **67**(6): p. 764-7.
101. Mirakhur, R.K., *Anticholinergic drugs in anaesthesia.* British Journal of Hospital Medicine, 1991. **46**(6): p. 409-11.
102. Mirakhur, R.K., *Preanaesthetic medication: a survey of current usage.* Journal of the Royal Society of Medicine, 1991. **84**(8): p. 481-3.
103. Stanley, J.C., et al., *Comparison of the haemodynamic effects of pipecuronium and pancuronium during fentanyl anaesthesia.* Acta Anaesthesiologica Scandinavica, 1991. **35**(3): p. 262-6.

104. Stanley, J.C., et al., *Neuromuscular effects of pipecuronium bromide.* European Journal of Anaesthesiology, 1991. **8**(2): p. 151-6.
105. Cooper, R., et al., *Effect of doxapram on the rate of recovery from atracurium and vecuronium neuromuscular block.[Erratum appears in Br J Anaesth 1992 Aug;69(2):xi].* British Journal of Anaesthesia, 1992. **68**(5): p. 527-8.
106. Cooper, R., et al., *Comparison of intubating conditions after administration of Org 9246 (rocuronium) and suxamethonium.* British Journal of Anaesthesia, 1992. **69**(3): p. 269-73.
107. Cooper, R.A., et al., *Estimation of the potency of ORG 9426 using two different modes of nerve stimulation.* Canadian Journal of Anaesthesia, 1992. **39**(2): p. 139-42.
108. Maddineni, V.R., et al., *Clinical evaluation of doxacurium chloride.* Anaesthesia, 1992. **47**(7): p. 554-7.
109. McCarthy, G., et al., *Onset and duration of action of vecuronium in the elderly: comparison with adults.* Acta Anaesthesiologica Scandinavica, 1992. **36**(4): p. 383-6.
110. McCarthy, G.J., et al., *Dose-response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly.* British Journal of Anaesthesia, 1992. **69**(3): p. 281-3.
111. McCarthy, G.J., R.K. Mirakhur, and P. Elliott, *Postoperative oxygenation in the elderly following general or local anaesthesia for ophthalmic surgery.* Anaesthesia, 1992. **47**(12): p. 1090-2.
112. McCarthy, G.J., R.K. Mirakhur, and S.K. Pandit, *Lack of interaction between propofol and vecuronium.* Anesthesia & Analgesia, 1992. **75**(4): p. 536-8.
113. McLoughlin, C., et al., *Muscle pains and biochemical changes following suxamethonium administration after six pretreatment regimens.* Anaesthesia, 1992. **47**(3): p. 202-6.
114. Mirakhur, R.K., *Newer neuromuscular blocking drugs. An overview of their clinical pharmacology and therapeutic use.* Drugs, 1992. **44**(2): p. 182-99.
115. Cooper, R., V.R. Maddineni, and R.K. Mirakhur, *Clinical study of interaction between rocuronium and some commonly used antimicrobial agents.* European Journal of Anaesthesiology, 1993. **10**(5): p. 331-5.

116. Cooper, R.A., et al., *Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure.* British Journal of Anaesthesia, 1993. **71**(2): p. 222-6.
117. Cooper, R.A., R.K. Mirakhur, and V.R. Maddineni, *Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anaesthesia.* Anaesthesia, 1993. **48**(2): p. 103-5.
118. Maddineni, V.R. and R.K. Mirakhur, *Prolonged neuromuscular block following mivacurium.* Anesthesiology, 1993. **78**(6): p. 1181-4.
119. Maddineni, V.R., R.K. Mirakhur, and A.R. Cooper, *Myalgia and biochemical changes following suxamethonium after induction of anaesthesia with thiopentone or propofol.* Anaesthesia, 1993. **48**(7): p. 626-8.
120. Maddineni, V.R., et al., *Potency estimation of mivacurium: comparison of two different modes of nerve stimulation.* British Journal of Anaesthesia, 1993. **70**(6): p. 694-5.
121. Maddineni, V.R., et al., *Neuromuscular effects and intubating conditions following mivacurium: a comparison with suxamethonium.* Anaesthesia, 1993. **48**(11): p. 940-5.
122. McCoy, E.P., et al., *Haemodynamic effects of rocuronium during fentanyl anaesthesia: comparison with vecuronium.* Canadian Journal of Anaesthesia, 1993. **40**(8): p. 703-8.
123. McCoy, E.P. and R.K. Mirakhur, *The levering laryngoscope.* Anaesthesia, 1993. **48**(6): p. 516-9.
124. McLoughlin, C.C., R.K. Mirakhur, and G.J. McCarthy, *Neuromuscular effects of succinylcholine following different pretreatments.* Journal of Clinical Anesthesia, 1993. **5**(1): p. 50-3.
125. Mirakhur, R.K., *New developments in nondepolarizing muscle relaxants.* Yale Journal of Biology & Medicine, 1993. **66**(5): p. 463-71.
126. Phillips, A.S., et al., *Propofol-fentanyl anaesthesia in cardiac surgery: a comparison in patients with good and impaired ventricular function.* Anaesthesia, 1993. **48**(8): p. 661-3.
127. Clarke, R.S. and R.K. Mirakhur, *Adverse effects of muscle relaxants.* Adverse Drug Reactions & Toxicological Reviews, 1994. **13**(1): p. 23-41.

128. Devlin, E.G., et al., *Effect of four i.v. induction agents on T-lymphocyte proliferations to PHA in vitro.* British Journal of Anaesthesia, 1994. **73**(3): p. 315-7.
129. Maddineni, V.R., R.K. Mirakhur, and E.P. McCoy, *Recovery of mivacurium block with or without anticholinesterases following administration by continuous infusion.* Anaesthesia, 1994. **49**(11): p. 946-8.
130. Maddineni, V.R., R.K. Mirakhur, and E.P. McCoy, *Plasma cholinesterase activity in elderly and young adults.* British Journal of Anaesthesia, 1994. **72**(4): p. 497.
131. Maddineni, V.R., et al., *Neuromuscular and haemodynamic effects of mivacurium in elderly and young adult patients.* British Journal of Anaesthesia, 1994. **73**(5): p. 608-12.
132. McCoy, E.P., et al., *Administration of rocuronium (Org 9426) by continuous infusion and its reversibility with anticholinesterases.* Anaesthesia, 1994. **49**(11): p. 940-5.
133. Mirakhur, R.K., *Safety aspects of non-depolarizing neuromuscular blocking agents with special reference to rocuronium bromide.* European Journal of Anaesthesiology - Supplement, 1994. **9**: p. 133-40.
134. Phillips, A.S., et al., *Propofol-fentanyl anesthesia: a comparison with isoflurane-fentanyl anesthesia in coronary artery bypass grafting and valve replacement surgery.* Journal of Cardiothoracic & Vascular Anesthesia, 1994. **8**(3): p. 289-96.
135. Chisakuta, A.M. and R.K. Mirakhur, *Anticholinergic prophylaxis does not prevent emesis following strabismus surgery in children.* Paediatric Anaesthesia, 1995. **5**(2): p. 97-100.
136. Connolly, F.M., et al., *Antagonism of mivacurium block with edrophonium from various degrees of spontaneous recovery.* British Journal of Anaesthesia, 1995. **74**(2): p. 229-30.
137. Cooper, R.A., et al., *Pharmacokinetics of rocuronium bromide in patients with and without renal failure.* European Journal of Anaesthesiology - Supplement, 1995. **11**: p. 43-4.
138. Devlin, E.G., et al., *The effects of thiopentone and propofol on delayed hypersensitivity reactions.* Anaesthesia, 1995. **50**(6): p. 496-8.

139. Loan, P.B., et al., *Comparison of the haemodynamic effects of mivacurium and atracurium during fentanyl anaesthesia.* British Journal of Anaesthesia, 1995. **74**(3): p. 330-2.
140. Loan, P.B., et al., *Comparison of desflurane and isoflurane in anaesthesia for dental surgery.* British Journal of Anaesthesia, 1995. **75**(3): p. 289-92.
141. Loan, P.B., et al., *The TOF-Guard neuromuscular transmission monitor. A comparison with the Myograph 2000.* Anaesthesia, 1995. **50**(8): p. 699-702.
142. McCarthy, G.J., et al., *Dose-responses for edrophonium during antagonism of vecuronium block in young and older adult patients.* Anaesthesia, 1995. **50**(6): p. 503-6.
143. McCoy, E.P., et al., *A new device for measuring and recording the forces applied during laryngoscopy.* Anaesthesia, 1995. **50**(2): p. 139-43.
144. McCoy, E.P., et al., *Nondepolarizing neuromuscular blocking drugs and train-of-four fade.* Canadian Journal of Anaesthesia, 1995. **42**(3): p. 213-6.
145. McCoy, E.P. and R.K. Mirakhur, *Comparison of the effects of neostigmine and edrophonium on the duration of action of suxamethonium.* Acta Anaesthesiologica Scandinavica, 1995. **39**(6): p. 744-7.
146. McCoy, E.P., et al., *The influence of the duration of control stimulation on the onset and recovery of neuromuscular block.* Anesthesia & Analgesia, 1995. **80**(2): p. 364-7.
147. McCoy, E.P., R.K. Mirakhur, and B.V. McCloskey, *A comparison of the stress response to laryngoscopy. The Macintosh versus the McCoy blade.* Anaesthesia, 1995. **50**(11): p. 943-6.
148. Mirakhur, R.K., *Spontaneous recovery or evoked reversal of neuromuscular block.* Acta Anaesthesiologica Scandinavica. Supplementum, 1995. **106**: p. 62-5.
149. Mirakhur, R.K., *Dose-response and time-course of action of rocuronium bromide.* European Journal of Anaesthesiology - Supplement, 1995. **11**: p. 23-5.
150. Mirakhur, R.K., *Accelerated onset of rocuronium.* Canadian Journal of Anaesthesia, 1995. **42**(5 Pt 1): p. 447-8.
151. Paxton, L.D., et al., *Intra-vas deferens bupivacaine for prevention of acute pain and chronic discomfort after vasectomy.* British Journal of Anaesthesia, 1995. **74**(5): p. 612-3.

152. Paxton, L.D., A.C. McKay, and R.K. Mirakhur, *Prevention of nausea and vomiting after day case gynaecological laparoscopy. A comparison of ondansetron, droperidol, metoclopramide and placebo.* Anaesthesia, 1995. **50**(5): p. 403-6.
153. Gilliland, H.E., et al., *An investigation of the potential morphine sparing effect of midazolam.* Anaesthesia, 1996. **51**(9): p. 808-11.
154. Kumar, N., et al., *A comparison of the effects of isoflurane and desflurane on the neuromuscular effects of mivacurium.* Anaesthesia, 1996. **51**(6): p. 547-50.
155. Kumar, N., et al., *Potency and time course of action of rocuronium during desflurane and isoflurane anaesthesia.* British Journal of Anaesthesia, 1996. **77**(4): p. 488-91.
156. McCoy, E.P., et al., *Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia.* British Journal of Anaesthesia, 1996. **76**(1): p. 29-33.
157. McCoy, E.P., et al., *A comparison of the forces exerted during laryngoscopy. The Macintosh versus the McCoy blade.* Anaesthesia, 1996. **51**(10): p. 912-5.
158. Phillips, A.S., et al., *Total intravenous anaesthesia with propofol or inhalational anaesthesia with isoflurane for major abdominal surgery. Recovery characteristics and postoperative oxygenation--an international multicentre study.* Anaesthesia, 1996. **51**(11): p. 1055-9.
159. Symington, M.J., et al., *Duration of stabilization of control responses affects the onset and duration of action of rocuronium but not suxamethonium.* European Journal of Anaesthesiology, 1996. **13**(4): p. 377-80.
160. Symington, M.J., R.K. Mirakhur, and N. Kumar, *Neostigmine but not edrophonium prolongs the action of mivacurium.* Canadian Journal of Anaesthesia, 1996. **43**(12): p. 1220-3.
161. Kelly, M.C., et al., *A comparison of the effect of intrathecal and extradural fentanyl on gastric emptying in laboring women.* Anesthesia & Analgesia, 1997. **85**(4): p. 834-8.
162. Loan, P.B., et al., *Neuromuscular effects of rocuronium in patients receiving beta-adrenoreceptor blocking, calcium entry blocking and anticonvulsant drugs.* British Journal of Anaesthesia, 1997. **78**(1): p. 90-1.

163. Mirakhur, R.K., *Potential morphine sparing effect of midazolam.* Anaesthesia, 1997. **52**(8): p. 803-4.
164. Mirakhur, R.K., *The interaction between mivacurium and rocuronium during onset and recovery.* Anaesthesia, 1997. **52**(3): p. 280.
165. Mirakhur, R.K., K.C. McCourt, and N. Kumar, *Use of intermediate acting muscle relaxants by infusion: the future.* Acta Anaesthesiologica Belgica, 1997. **48**(1): p. 29-34.
166. Carroll, M.T., et al., *A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium.* Anaesthesia, 1998. **53**(8): p. 744-8.
167. Carroll, M.T., et al., *Neuromuscular blocking effects and train-of-four fade with cisatracurium: comparison with other nondepolarising relaxants.* Anaesthesia, 1998. **53**(12): p. 1169-73.
168. Kelly, M.C., U.A. Carabine, and R.K. Mirakhur, *Intrathecal diamorphine for analgesia after caesarean section. A dose finding study and assessment of side-effects.* Anaesthesia, 1998. **53**(3): p. 231-7.
169. Lowry, D.W., et al., *Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia.* Anesthesia & Analgesia, 1998. **87**(4): p. 936-40.
170. McCourt, K.C., et al., *Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia.* Anaesthesia, 1998. **53**(9): p. 867-71.
171. Mirakhur, R.K. and M. Morgan, *Intravenous anaesthesia: a step forward.* Anaesthesia, 1998. **53 Suppl 1**: p. 1-3.
172. Lowry, D.W., et al., *Comparison of sevoflurane and propofol with rocuronium for modified rapid-sequence induction of anaesthesia.* Anaesthesia, 1999. **54**(3): p. 247-52.
173. Lowry, D.W., et al., *Potency and time course of mivacurium block during sevoflurane, isoflurane and intravenous anesthesia.* Canadian Journal of Anaesthesia, 1999. **46**(1): p. 29-33.
174. McCourt, K.C., et al., *Haemodynamic effects of rapacuronium in adults with coronary artery or valvular disease.* British Journal of Anaesthesia, 1999. **83**(5): p. 721-6.
175. McCourt, K.C., R.K. Mirakhur, and C.M. Kerr, *Dosage of neostigmine for reversal of rocuronium block from two levels of spontaneous recovery.* Anaesthesia, 1999. **54**(7): p. 651-5.

176. McCourt, K.C., et al., *Spontaneous or neostigmine-induced recovery after maintenance of neuromuscular block with Org 9487 (rapacuronium) or rocuronium following an initial dose of Org 9487.* British Journal of Anaesthesia, 1999. **82**(5): p. 755-6.
177. O'Hare, R., et al., *Bolus dose remifentanil for control of haemodynamic response to tracheal intubation during rapid sequence induction of anaesthesia.* British Journal of Anaesthesia, 1999. **82**(2): p. 283-5.
178. Blobner, M., et al., *Rapacuronium 2.0 or 2.5 mg kg-1 for rapid-sequence induction: comparison with succinylcholine 1.0 mg kg-1.* British Journal of Anaesthesia, 2000. **85**(5): p. 724-31.
179. Breslin, D., et al., *Anaesthesia in myotubular (centronuclear) myopathy.* Anaesthesia, 2000. **55**(5): p. 471-4.
180. Elliott, P., et al., *Severe cardiovascular depression with remifentanil.* Anesthesia & Analgesia, 2000. **91**(1): p. 58-61.
181. Hayes, A., et al., *Comparison of recovery following rapacuronium, with and without neostigmine, and succinylcholine.* Anaesthesia, 2000. **55**(9): p. 859-63.
182. Proost, J.H., et al., *Urinary, biliary and faecal excretion of rocuronium in humans.* British Journal of Anaesthesia, 2000. **85**(5): p. 717-23.
183. Reid, J.E. and R.K. Mirakhur, *Bradycardia after administration of remifentanil.* British Journal of Anaesthesia, 2000. **84**(3): p. 422-3.
184. Breslin, D.S., et al., *Sevoflurane--nitrous oxide anaesthesia supplemented with remifentanil: effect on recovery and cognitive function.* Anaesthesia, 2001. **56**(2): p. 114-9.
185. Hayes, A.H., et al., *Frequency of haemoglobin desaturation with the use of succinylcholine during rapid sequence induction of anaesthesia.* Acta Anaesthesiologica Scandinavica, 2001. **45**(6): p. 746-9.
186. Hayes, A.H., et al., *Postoperative residual block after intermediate-acting neuromuscular blocking drugs.* Anaesthesia, 2001. **56**(4): p. 312-8.
187. Mirakhur, R.K. and K.C. McCourt, *Rapacuronium: clinical pharmacology.* European Journal of Anaesthesiology - Supplement, 2001. **23**: p. 77-82.
188. O'Hare, R.A., et al., *Recovery from propofol anaesthesia supplemented with remifentanil.* British Journal of Anaesthesia, 2001. **86**(3): p. 361-5.

189. Reid, J.E., et al., *Neostigmine antagonism of rocuronium block during anesthesia with sevoflurane, isoflurane or propofol.* Canadian Journal of Anaesthesia, 2001. **48**(4): p. 351-5.
190. Wierda, J.M. and R.K. Mirakhur, *Current developments in anaesthesia and neuromuscular transmission.* European Journal of Anaesthesiology - Supplement, 2001. **23**: p. 1-3.
191. Breslin, D.S., P.A. Farling, and R.K. Mirakhur, *The use of remifentanil in the anaesthetic management of patients undergoing adrenalectomy: a report of three cases.* Anaesthesia, 2003. **58**(4): p. 358-62.
192. McMorrow, R.C.N. and R.K. Mirakhur, *A new mirrored laryngoscope.* Anaesthesia, 2003. **58**(10): p. 998-1002.
193. Breslin, D.S., et al., *Manual versus target-controlled infusions of propofol.* Anaesthesia, 2004. **59**(11): p. 1059-63.
194. Shields, M., et al., *Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block.* British Journal of Anaesthesia, 2006. **96**(1): p. 36-43.
195. Shields, M.O., et al., *The use of basophil activation to diagnose allergy to Gelofusine.* Anaesthesia, 2006. **61**(7): p. 716-7; author reply 717-8.
196. Fuchs-Buder, T., et al., *Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision.* Acta Anaesthesiologica Scandinavica, 2007. **51**(7): p. 789-808.
197. McDermott, B.J., et al., *Protection of cardiomyocyte function by propofol during simulated ischemia is associated with a direct action to reduce pro-oxidant activity.* Journal of Molecular & Cellular Cardiology, 2007. **42**(3): p. 600-8.
198. Flockton, E.A., et al., *Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine.* British Journal of Anaesthesia, 2008. **100**(5): p. 622-30.
199. Hogg, R.M.G. and R.K. Mirakhur, *Sugammadex: a selective relaxant binding agent for reversal of neuromuscular block.* Expert Review of Neurotherapeutics, 2009. **9**(5): p. 599-608.
200. Mirakhur, R.K., *Sugammadex in clinical practice.* Anaesthesia, 2009. **64 Suppl 1**: p. 45-54.

201. Mirakhur, R.K. and W. Harrop-Griffiths, *Management of neuromuscular block: time for a change?* Anaesthesia, 2009. **64 Suppl 1**: p. iv-v.
202. Plaud, B., et al., *Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients.* Anesthesiology, 2009. **110**(2): p. 284-94.
203. Mirakhur, R.K., *A survey of practice of neuromuscular block in the United States and Europe.* Anesthesia & Analgesia, 2011. **112**(2): p. 481; author reply 482-3.
204. Mirakhur, R.K., M.O. Shields, and H.D. de Boer, *Sugammadex and rescue reversal.* Anaesthesia, 2011. **66**(2): p. 140-1; author reply 141.