Clinical relaxation: current controversy

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Several topics of current interest in the field are currently undergoing evolution. Since we are living and practicing in the midst of this change, there is controversy surrounding the adaptation of new concepts and procedures into clinical practice.

This lecture will discuss the following areas of current discussion.

- 1 The "priming" technique, onset of neuromuscular blockade, rapidity of intubation, and intubating conditions using nondepolarizing relaxants.
- 2 Reversal of neuromuscular blockade:
 - reversal of very deep nondepolarizing block: special considerations.
 - reversal of the new intermediate-duration nondepolarizers: is it always necessary?
 - reversal of phase II block after succinylcholine infusion.
- 3 Infusions of nondepolarizing relaxants.
- 4 New nondepolarizing relaxants in clinical trial at present:

BW A938U	} Long-acting nondepolarizers free of side effects.
Pipecuronium	
BW B1090U, a short-acting nondepolarizer.	
- 5 Metabolites of atracurium and vecuronium and their potential pharmacological effects.

The priming technique, onset of block, speed of intubation, and intubating conditions¹⁻⁴

"Priming," as originally proposed by several authors, does, in my opinion, speed the achievement of intubating conditions by 30-60 seconds when using nondepolarizing relaxants.

A good general rule is as follows: the safest yet most effective priming dose of nondepolarizer is about ten per cent the size of typical doses advised for elective non-emergency intubations. Twenty per cent is too high a dose (since about 10-20 per cent of subjects given this size dose will show definite symptoms or signs of weakness within two or three minutes). By "priming" as above, non-emergent elective intubation may be accomplished under excellent conditions within two minutes,

provided that all of the steps outlined below are followed (see Table I).

Can true "rapid-sequence" emergency intubation be accomplished with a nondepolarizer? Again, I believe the answer is yes, if the clinician is willing to follow the steps outlined below, and if the clinician accepts 90 seconds after injection of the "intubating" dose of relaxants as the intubation time. In emergency situations, however, the "intubating dose" should be increased by 25-50 per cent (Table I).

Reversal of neuromuscular blockade⁵⁻⁷

Reversal of very deep nondepolarizing block

A number of recent studies emphasize that special care must be taken during reversal of very deep block. If one twitch or less is present during train-of-four monitoring at the time of reversal, then it is likely that adequate reversal will take 20 minutes or more. Large doses of neostigmine (0.06-0.08 mg·kg⁻¹) should be given in this situa-

TABLE I Suggested priming sequence* for accelerated tracheal intubation using nondepolarizing relaxants

Drug	Priming dose (mg·kg ⁻¹)	Priming interval (min)	Dosage (mg·kg ⁻¹) for	
			Routine intubation (2 min)	"Rapid sequence" (90 sec)
Atracurium	0.06	4-6	0.5	0.75
Vecuronium	0.01	4-6	0.1	0.15
Pancuronium	0.01	4-6	0.1	0.15
Metocurine	0.05	4-6	0.3	0.5

*Sequence suggested assumes that adequate dosage of premedication and intravenous induction agents has been administered prior to administration of relaxants.

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TABLE II Infusion dosage requirement for maintenance of 90–95% block

Drug	Dose ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)*
Atracurium	6–8	380
Vecuronium	1–2	100

*From Gramstad and Lilleaasen (1985).

tion. Neostigmine is a better antagonist than edrophonium in this circumstance.

Reversal of intermediate-duration nondepolarizers

Some experts advise administration of anticholinesterases at the end of every case when atracurium or vecuronium has been used. While this philosophy is no doubt a safe one, it evades the issue that, in carefully monitored patients given carefully selected doses of these drugs, spontaneous recovery is often adequate at the end of a high percentage of cases, particularly if dosing is properly timed. Reversal of these drugs, which have the advantage of rapid spontaneous recovery patterns, should be done on indication rather than as a routine. This difference in philosophy will be discussed.

Reversal of phase II block

A number of recent papers have shown that successful reversal of phase II block using anticholinesterases nearly always is possible. The philosophy regarding proper clinical management of a slowly recovering phase II block after succinylcholine should be as follows:

- Proper diagnosis: fade of train-of-four or fade of tetanus
- Proper treatment: neostigmine ($0.03\text{ mg}\cdot\text{kg}^{-1}$) or edrophonium ($0.3\text{ mg}\cdot\text{kg}^{-1}$) should markedly accelerate the recovery pattern. However, conservative airway management for at least one hour following anticholinesterase administration should still be emphasized.

Infusions of nondepolarizing relaxants^{8–14}

Both atracurium and vecuronium may readily be administered as continuous infusions to maintain stable levels of neuromuscular blockade for several hours. This should be done with careful monitoring. Administration by infusion pump is helpful but not absolutely necessary. Average infusion requirements during balanced anaesthesia are listed in

Table II. The dosage may be reduced by 20–30 per cent during inhalation anaesthesia.

New nondepolarizing relaxants^{15–19}

Three new nondepolarizing relaxants are in various stages of clinical evaluation at present. Their actions and clinical advantages will be discussed in some detail. Their clinical pharmacology is outlined in Table III.

Metabolites of nondepolarizing relaxants^{20–28}

Atracurium is metabolized via either Hofmann Elimination or ester hydrolysis to multiple breakdown products. Two of these, the ultimate products of either pathway, are *laudanosine* and *pentamethylene diacrylate*. The putative breakdown products of atracurium were shown by Chapple and Clark²⁰ to have no measurable neuromuscular or cardiovascular effect at dosage many multiples higher than possible during clinical

Laudanosine has been correctly identified as a possible CNS stimulant. This metabolite is measurable in the plasma within a few minutes after atracurium injection. It has been shown during animal studies that while large intravenous bolus doses of laudanosine may excite the central nervous system, the plasma concentrations necessary to cause this effect are virtually unattainable during clinical use of the parent compound, atracurium.

Pentamethylene diacrylate, the other metabolite, has raised a single note of concern. Nigrovic and Koechel²¹ pointed out that some acrylic esters have shown mutagenic effects in animals. However, the Ames test for atracurium does not show any mutagenic property for the parent compound or any possible metabolites (Skarpa *et al.*²²).

Vecuronium also undergoes a moderate degree of metabolism. It is de-acetylated at the 3 and 17 positions, probably by microsomal enzymes in the liver. The putative metabolites, 3-OH, 17-OH, and 3,17-OH vecuronium, have no central nervous system or cardiovascular effect. The 3-OH metabolite, however, is about 80 per cent as potent as the parent compound. Whether this metabolite accumulates or not has not yet been proven.

The metabolism of the new nondepolarizer BW B1090U has not yet been extensively studied. Possible metabolic pathways and possible actions of putative metabolites will be discussed.

TABLE III New nondepolarizing relaxants

Drug	Class	Potency (ED95) (mg·kg ⁻¹)	Intubating dose (mg·kg ⁻¹)	Onset
Pipecuronium	Steroid	0.05	0.08	3–5 min
BW A938U	Benzylisoquinolinium	0.025	0.05	3–5 min
BW B1090U	Benzylisoquinolinium	0.09	0.15–0.25	1.5–2.5 min

Drug	Duration to 95% recovery	Clinical Duration (to 25% recovery)	Maintenance	Reversible?
Pipecuronium	2–4 hours	1–1½ hours	repeat bolus	yes
BW A938U	2–4 hours	1–1½ hours	repeat bolus	yes
BW B1090U	25–35 min	15–25 min	infusion	yes

Drug	Preparation	Elimination	Cardiovascular effects
Pipecuronium	Solid	Kidney	Minimal
BW A938U	Solution	Kidney ?Plasma ChE	Minimal
BW B1090U	Solution	Plasma ChE ?Liver	Weak histamine release

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