

The New Neuromuscular Blocking Drugs Are Here

THERE is a well-recognized clinical need for new nondepolarizing relaxants of shorter duration, less cumulative propensity, and fewer side effects than presently available drugs. Three hypothetical materials which would provide significant advances in relaxant therapeutics were described six years ago¹ (fig. 1). Now, several new substances which do possess the desirable properties hypothesized above have been produced and are in various stages of clinical trial. These new relaxants will no doubt change our patterns of practice by improving the safety and versatility of clinical relaxation.

In this issue of ANESTHESIOLOGY, Fahey *et al.*² present the first clinical evaluation in the United States of one of these new substances, ORG NC45 (NorcuronTM), a new pancuronium analogue. In addition, a detailed comparative study of the relative neuromuscular and vagal blocking properties of ORG NC45 and its parent compound, pancuronium, is offered by Lee-Son *et al.*³

How does ORG NC45 compare with other nondepolarizing neuromuscular blocking drugs? All evaluations of ORG NC45 *vs.* pancuronium, *d*-tubocurarine, and other currently used nondepolarizers, both in animals and in humans, indicate that the new drug has the following advantages: 1) shorter duration of action—the duration is approximately 35–40 per cent that of pancuronium;^{2,4} 2) a significant lack of cardiovascular effect—the new drug has less than one-twentieth the vagolytic effect of pancuronium,⁵ and consequently does not appear to produce tachycardia at clinical dosage;⁴ and 3) less cumulative tendency than other nondepolarizing relaxants in current use.^{2,4}

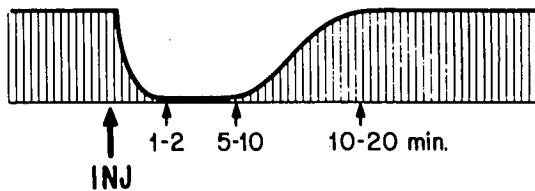
There do not appear to be any major disadvantages, although it is somewhat disappointing that the onset of block by ORG NC45 does not seem to be significantly faster than other nondepolarizers at dosages required for abdominal relaxation or for tracheal intubation in the absence of potent anesthetic vapors (approximately 0.05 and 0.10 mg/kg, respectively).^{2,4} It is possible to produce a faster onset, however, by an increase in dosage (≥ 0.14 mg/kg) as shown by Fahey *et al.*,² apparently without producing any important cardiovascular effect, but with the consequence of a considerably longer duration of action.

ORG NC45 is an excellent example of how an apparently minor molecular change may result in significant alteration of pharmacologic activity. Chemically, the drug is simply pancuronium without the quaternizing methyl group in the 2-piperidino substitution (see Fahey *et al.*² and fig. 1), hence the trade name Norcuron.TM ORG NC45 is, therefore, a monoquaternary substance (although the tertiary amine at position 2 is probably protonated in the physiologic pH range). This seemingly minor chemical difference is responsible for all of the considerable pharmacologic differences between ORG NC45 and pancuronium: 1) the absence of this methyl group reduces the acetylcholine-like character of the molecule in the area of ring "A" of the steroid nucleus, thereby lessening its vagolytic property without loss of neuromuscular blocking activity; the 16 β -piperidinium and 17 β -acetoxy substitutions (the ring "D" substituents) are retained intact from pancuronium and are apparently responsible for high neuromuscular blocking potency but not for the vagolytic effect;^{5,6} and 2) the presence of the tertiary amine in ring "A" increases the lipophilic nature of the molecule, thereby no doubt rendering it more susceptible to metabolism by liver microsomes, which require lipid substrates. Increased liver metabolism may be one reason for the

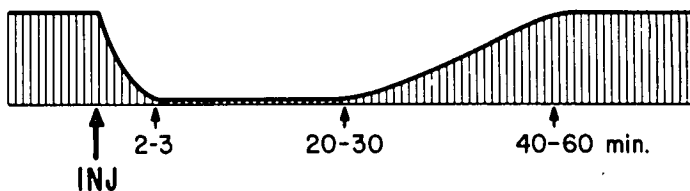
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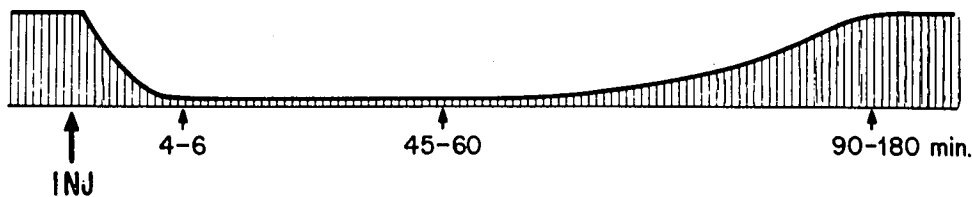
A. Short-acting non-depolarizing agent



B. Intermediate-duration noncumulative non-depolarizing agent



C. Long-duration non-depolarizing agent devoid of cardiovascular side effects



shorter duration of action of ORG NC45 compared to pancuronium.

ORG NC45 is one of several new relaxants currently undergoing clinical evaluation which appear to be actively metabolized within the body to relatively inactive derivatives. The new nondepolarizers, therefore, have shorter durations of action and less cumulative effect than current drugs, as well as being less dependent on the kidney for elimination. Two more new nondepolarizers now under clinical trial which also seem to offer durations of action of approximately one-third that of pancuronium or *d*-tubocurarine, lack of cumulative tendency, and lack of cardiovascular effect are BW33A (Atracurium)⁷⁻¹⁰ and BWA444U.*¹¹ Their routes of metabolism are different from that of ORG NC45: Atracurium is metabolized by Hoffman elimination and ester hydrolysis⁷ and BWA444U is hydrolyzed by plasma cholinesterase.¹¹

ORG NC45, Atracurium,[®] and BWA444U may be classified as intermediate-duration noncumulative nondepolarizing relaxants of the "B" type (fig. 1). A "C"

type drug also appears to be available: pipecurium, a long-acting pancuronium analogue, is reportedly free of side effects.^{12,13} Only the "A" type short-acting nondepolarization is not available. Such a drug is certainly possible in humans, however, as shown by the recent unsuccessful clinical trial of BW785U. The latter agent did produce nondepolarizing block with "A" type onset and duration, but released too much histamine to be routinely applicable to humans.^{14,15}

How will our clinical practice patterns be changed by these new relaxants? First, anesthetists will have the option of fitting the relaxant's metabolic pathway to the individual patient. This will necessitate a more detailed understanding of the new relaxant's metabolism than our accustomed considerations of current nondepolarizers. Second, our awareness of relaxant side effects (cardiovascular effects) may diminish, since the effects of the new drugs on arterial pressure and heart rate are so minimal. In fact, we can now expect that any new neuromuscular blocker must be free of side effects to merit clinical usage. Third, in order to use the new drugs to their greatest advantage, clinical monitoring of neuromuscular function must become

FIG. 1. Three hypothetical non-depolarizing neuromuscular blocking agents which would improve the versatility and safety of clinical relaxation were described six years ago.¹ Now the need for drug "B", the intermediate-duration noncumulative nondepolarizing relaxant, has been filled by ORG NC45, as well as by two more materials, BW33A (Atracurium[®]) and BWA444U, all of which are in clinical trial at the present time. Such agents provide intubating conditions within 2-3 min, show initiation of recovery within 20-30 min, and complete recovery within 40-60 min. Pipecurium, a long-acting pancuronium analogue, fits the description of drug "C". Only the "A"-type drug is not in clinical trial at present. See text for further details.

* Savarese JJ, Basta SJ, Ali HH: Data in preparation.

more important. This is necessary since on the one hand it will be easy to overdose with the new agents because their side effects are minimal. On the other hand, many operations may be performed without the need for reversal of residual block (because recovery is relatively rapid) if supplemental doses of the new drugs are precisely timed as indicated by monitoring techniques. Train-of-four monitoring¹⁶ and counting of the number of responses visible in the train¹⁷ will be just as applicable in the case of the new nondepolarizers as in the use of current drugs. Fourth, intubation of the trachea with nondepolarizing relaxants will become more common, since the new intermediate-duration agents make it possible to achieve the depth of paralysis required for this maneuver without the consequence of very long-duration neuromuscular blockade. For those anesthesiologists still preferring succinylcholine for intubation because of its fast onset and the convenience of fasciculations heralding the onset of block, the new intermediate-duration nondepolarizers will still provide convenient maintenance of relaxation after intubation because of their lack of cumulative tendency. In fact, this property has already suggested⁴ that maintenance of relaxation by continuous infusion of noncumulative nondepolarizing relaxants may become commonplace.

The new relaxants are part of a wave of pharmacologic innovation currently sweeping our specialty. Together with new narcotic analgesics, new induction agents, and new inhalation anesthetics, the new neuromuscular blocking drugs promise to revolutionize the practice of anesthesia.

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Anaphylactoid Reactions to Anesthetic Drugs

HISTAMINE is distributed throughout the human body and is present in potentially lethal quantities in organs that are particularly vulnerable to its actions, *e.g.*, the

airways, blood vessels, and heart. Most of it is sequestered with heparin in small membrane-bound granules in mast cells (3-20 pg histamine/cell). These cells are embedded in the mucosal linings, skin, connective tissue, adventitia of small blood vessels, and

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