"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

RESISTANCE TO NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

Most anaesthetists have had the clinical experience of being unable to produce adequate neuromuscular block for surgical access despite repeated, and what occasionally might be considered excessive, doses of a non-depolarizing neuromuscular blocking agent. The cause of this resistance usually remains unexplained at the end of surgery and cannot be clarified by routine plasma screening. Sometimes apparent resistance results from no factor more complicated than simple error: failure to store the drug at the recommended temperature, errors in dilution, or even use of the wrong substance. When these simple possibilities have been excluded, altered plasma protein binding or volume of distribution should be considered. The effect of an increased number of postsynaptic acetylcholine receptors may also be relevant, as may the patient's temperature and metabolic state or the isomeric mixture of the drug in the vial.

Plasma protein binding

Most drugs bind to at least one of three plasma proteins: *albumin* (which has three separate binding sites), *alpha$_1$ acid glycoprotein* (AAG) (one of the alpha$_1$ globulins) or *lipoproteins* [1]. Drugs may bind to more than one site on the albumin molecule and to more than one plasma protein. In general, acidic drugs are believed to bind to albumin and basic drugs to AAG [2]. It would be expected that non-depolarizing neuromuscular blocking agents, with their basic quaternary amine structure, would bind predominantly to AAG, but Stovner, Theodorsen and Bjelke suggested in 1971 that alcuronium [3] and gallamine [4] are bound predominantly to plasma albumin, in contrast with pancuronium [4], for which no specific binding pattern could be detected. Baraka and Gabali [5] found a highly significant correlation between the serum concentration of gamma globulin and tubocurarine requirement, with a weaker relationship to the albumin concentration. It seems, therefore, that even the basic principles of binding of drugs to plasma proteins cannot be applied simply to non-depolarizing neuromuscular blocking agents. Measuring plasma protein binding is fraught with problems, however [1], and the validity of many of the earlier reports is questionable. For example, it may have been difficult to differentiate between alpha$_1$ and gamma globulin in earlier studies, and this would explain the discrepancy with tubocurarine. More research is clearly needed on plasma protein binding of neuromuscular blocking agents.

It is important to remember that the total plasma protein binding of neuromuscular blocking drugs compared with such drugs as diazepam (98%) and alfentanil (92%) [1] is not great (table I). In practice, changes in the degree of plasma protein binding are of clinical importance only if protein binding is greater than 85%, when only a small decrease in the amount of bound drug increases to a highly significant degree the free fraction of the drug, which is responsible for the clinical effect [1, 2]. Because non-depolarizing drugs are not highly bound, any slight change in the degree of protein binding of a neuromuscular blocking agent is unlikely to be of clinical significance.

Clinical resistance is seen most often in chronic disease, but no change in the plasma protein binding of pancuronium [8] or tubocurarine [9]

TABLE I. *Plasma protein binding of the non-depolarizing neuromuscular blocking agents [1, 6, 7]. * By an indirect* in vitro *method [7]; † [unpublished data: J. M. Hunter and T. N. Calvey]*

	Percent bound
Alcuronium	40
Atracurium	?82*
	37†
Pancuronium	11–29
Tubocurarine	43–51
Vecuronium	30

TABLE II. *Volume of distribution of non-depolarizing neuromuscular blocking agents in health and disease (mean values);* * $P < 0.05$ *compared with healthy group*

	Volume of distribution (ml kg^{-1})					
	Renal effects			Hepatic effects		
	Healthy	Chronic renal failure	Ref.	Healthy	Cirrhotic liver disease	Ref.
Atracurium	182	224	[16]	202	282*	[17]
Pancuronium	262	296	[18]	279	416*	[19]
Vecuronium	194	239	[20]	246	253	[21]

has been found in renal disease, or of tubocurarine [9], pancuronium or vecuronium [6] in cirrhotic liver disease, although plasma protein concentrations are known to alter in these circumstances. However, altered binding of basic drugs to AAG in acute disease states may explain the resistance to atracurium reported in this issue by Tatman, Wrigley and Jones [10]. Plasma concentrations of AAG, an acute phase protein, are increased in several acute conditions, including burns, myocardial infarction, severe infection, malignancy, Crohn's disease, ulcerative colitis and renal transplantation [1]. They are increased also in some types of chronic renal failure [2]. This increased binding to an acute phase protein, with a subsequent reduction in the free, active fraction of the drug may explain, therefore, the occasional unexpected difficulty in obtaining adequate neuromuscular block, especially during emergency surgery; but whether it is responsible for the hyposensitivity to tubocurarine demonstrated after thermal injury has been questioned [11].

Altered volume of distribution

Since the first report by Dundee and Gray [12], it has been demonstrated that patients with cirrhotic liver disease, of various aetiologies, are resistant to small bolus doses, not only of tubocurarine but also of pancuronium [13], atracurium and vecuronium [14]. There is some evidence of a similar resistance in chronic renal failure [15]. This phenomenon may be caused, not by an increase in the protein binding of the neuromuscular blocking agent which would *decrease* the volume of distribution of the drug, but by an *increased* volume of distribution of these water soluble, highly ionized drugs in conditions in which there is a significant increase in extracellular fluid, with or without frank oedema. The increased volume of distribution of a bolus dose of a neuromuscular blocking agent is associated with a smaller plasma concentration and hence a reduced effect. Repeated increments of the blocking drug eventually increase the plasma concentration sufficiently to produce satisfactory clinical conditions, but difficulty in eventual antagonism of residual neuromuscular block may ensue because of delayed clearance of the relaxant caused by the disease state. The volumes of distribution of some non-depolarizing neuromuscular blocking agents in health and disease are shown in table II.

Increased number of receptor sites

Where resistance to non-depolarizing neuromuscular blocking agents has been reported in chronic disease states involving voluntary muscle, a pharmacodynamic rather than a pharmacokinetic problem is envisaged. The affected muscles in hemiplegia, for example, are thought to be resistant because of increase in postsynaptic acetylcholine receptors [22], as is possibly the case in multiple sclerosis [23] and disuse atrophy [24]. In these chronic conditions, however, the anaesthetist is usually aware of the pre-existing pathology and should not, therefore, experience *unexpected* resistance to a non-depolarizing neuromuscular blocking drug. In many muscle disorders, such as myasthenia gravis and myotonia dystrophica, increased sensitivity to non-depolarizing blockers is common but, because both *upgrading* and *downgrading* of postsynaptic acetylcholine receptors can occur in these conditions, resistance may occasionally be encountered.

Treatment with the antiepileptic drug phenytoin, has been associated with resistance to all the non-depolarizing neuromuscular blockers, except atracurium. It has been postulated that this may

be caused by an increase in the number of postsynaptic receptors, a decrease in their sensitivity or even a presynaptic effect [25].

Body temperature and pH

It is interesting to speculate on the relationship between an increase in body temperature and the degree of block obtained by the non-depolarizing neuromuscular blocking agents. From animal work it has been suggested that an increase in temperature may reduce the duration of action of atracurium, as Hofmann elimination is potentiated [26], but in such circumstances it may be that increased binding of not only atracurium but all these drugs to acute phase proteins is a factor in the decreased duration of action occasionally encountered in pyrexial patients.

A respiratory alkalosis has been shown to antagonize the neuromuscular block produced by tubocurarine [27], pancuronium and vecuronium [28], although the effect of metabolic alkalosis is more controversial; indeed, it has been suggested that the latter may potentiate the block. Hyperkalaemia may also be expected to decrease the duration of drug-induced neuromuscular block, as it lowers the resting membrane potential of the muscle membrane, thus promoting depolarization and muscle contraction.

Isomeric mixtures

A vial of any optically active drug may contain more than one isomer; each isomer may have a different elimination half-life and rate of clearance from the body. A vial of atracurium may contain up to 10 isomers. The three geometrical isomer groups present are the cis–cis, cis–trans and trans–trans groups. The cis–cis group (58%), which produces the required clinical effect, has a half-life of about 23 min. The cis–trans group (36%) has a biexponential half-life with a rapid phase of 2.3 min and the trans–trans group (6%) has such a short half-life that, in the small concentrations found in the plasma after a bolus injection, it is difficult to measure [29]. If the last two of these isomers are present in greater than expected concentrations in a vial, more rapid than expected recovery may occur. This is, however, an unlikely cause of unexpected resistance to atracurium and the resistance is only apparent, not real.

J. M. Hunter

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