

# Hemodynamic effects of muscle relaxants

Anis Baraka, M.D.

*Beirut, Lebanon*

The hemodynamic effects of neuromuscular blocking drugs (muscle relaxants) may be attributed to two basic mechanisms: (1) histamine release; and (2) acetylcholinelike effects that may be central, neuromuscular, or autonomic.

## **Histamine release**

In 1939, Alam et al<sup>1</sup> demonstrated for the first time that intraarterial injection of *d*-tubocurarine in dogs resulted in release of histamine. Considerable range of organic bases can directly mobilize histamine from its bound state in the mast cells.<sup>2</sup> All muscle relaxants may stimulate histamine release. The most important relaxant in this connection is *d*-tubocurarine.<sup>3</sup> This direct histamine-releasing effect can be clinically important in atopic patients. In contrast with this direct effect, the histamine release that follows antigen-antibody reaction is not limited to *d*-tubocurarine, and has been reported with other relaxants.

## **Acetylcholinelike effects**

Neuromuscular blocking agents are structurally similar to acetylcholine. They are positively charged quaternary ammonium compounds, which mimic or compete with acetylcholine at the central, neuromuscular, and autonomic cholinergic sites.

**Central sites.** Muscle relaxants are ionized hy-

drophilic molecules that do not cross readily the blood-brain barrier. However, Piess and Manning<sup>4</sup> found that moderate doses of curare have a central action on the mechanism controlling cardiovascular function. Also, Forbes et al<sup>5</sup> showed that pancuronium reduces halothane requirements in man. These effects can be explained by considering the blood-brain barrier as a relative and not an absolute barrier, which can allow the passage of relaxants. Following intravenous injection, the intrathecal concentration of *d*-tubocurarine is about 1/1000 the plasma concentration.<sup>6</sup> Both nicotinic and muscarinic cholinergic pathways exist in the central nervous system, and may be inhibited by relaxants.<sup>7-10</sup>

**Neuromuscular effects.** The hemodynamic effects of muscle relaxants may also be secondary to the neuromuscular effects. The loss of muscle tone and peripheral pooling of blood, together with the initiation of intermittent positive respiration, can greatly impede venous return and lower cardiac output. That is why relaxants that lack histamine release or autonomic side effects, such as metocurine and alcuronium, may lower the blood pressure.<sup>11</sup>

In contrast, the initial muscle fasciculation associated with depolarizing relaxants such as succinylcholine can augment venous return. Also, the supersensitivity response of denervated muscles, extensive burns, massive trauma, and severe sepsis to succinylcholine can induce massive hyperkalemia and trigger serious cardiac arrhythmias.<sup>12-18</sup>

**Autonomic side effects.** Neuromuscular blocking drugs can be classified according to their effect on autonomic transmission. A clear understanding of autonomic transmission is the basis of such classification.

Acetylcholine is the chemical trans-

mitter at the neuromuscular junction, at the ganglia of both sympathetic and parasympathetic systems (nicotinic), and at the muscarinic postsynaptic receptors. In analogy with the different adrenergic receptors, it appears that nicotinic and muscarinic receptors vary according to the target organs. Nicotinic receptors at the neuromuscular junction may be different from those present at the ganglia, and muscarinic receptors of the heart may be different from muscarinic receptors present elsewhere.

Muscle relaxants either mimic (agonists) or block the effect (antagonists) of acetylcholine not only at the neuromuscular junction, but also on these autonomic cholinceptive sites.

### Agonists

Succinylcholine, consisting of two acetylcholine molecules linked together, appears to display all stimulating effects of the chemical transmitter on both the nicotinic and muscarinic cholinergic receptors.<sup>3</sup> The net effect is a balance of the two actions. After the first dose of succinylcholine, the nicotinic effect usually predominates and results in hypertension, tachycardia, and arrhythmia. However, after repeated doses and sometimes after the first dose, the muscarinic effect predominates and manifests itself as bradycardia.<sup>19-24</sup> Bradycardia can even be observed in isolated hearts denoting a direct muscarinic effect of succinylcholine on the pacemaker.<sup>25</sup> It can be prevented by prior administration of an anticholinergic drug or a pretreatment dose of nondepolarizing relaxant.

### Antagonists

Nondepolarizing relaxants can have different autonomic effects<sup>26</sup>: (1) No or minimal autonomic effects, e.g., dimethyl tubocurarine (metocurine) and

diallylnortoxiferine (alcuronium). (2) Nicotinic blockers, e.g., *d*-tubocurarine. (3) Muscarinic blockers, e.g., gallamine, pancuronium. Org NC45, a homologue of pancuronium was found to have fewer autonomic effects than that of pancuronium.<sup>27</sup>

The dose-ratio of autonomic to neuromuscular block has been termed the "autonomic margin of safety,"<sup>28-30</sup> and is equal to:

$$\frac{\text{ED 50 for vagal and sympathetic inhibition}}{\text{ED 95 for neuromuscular blockade}}$$

Neuromuscular blocking drugs can be classified according to their "autonomic margin of safety" into two categories:

### 1. High autonomic margin of safety

The drug will show a wide separation of neuromuscular block from its autonomic side effects, e.g., dimethyl tubocurarine and diallylnortoxiferine.

Dimethyl tubocurarine (metocurine) is a bis-quaternary ammonium molecule having no ganglionic blocking or histamine-releasing properties. Thus, it has a high autonomic safety margin. The drug is produced as a result of methylation of the parent relaxant *d*-tubocurarine at the tertiary amine and at the hydroxyl groups.

Diallylnortoxiferine (alcuronium) is also a bis-quaternary ammonium compound, which does not block ganglionic transmission or release histamine. Its neuromuscular block is only associated with mild vagal blockade.

### 2. Low autonomic margin of safety

The drug will have autonomic side effects in doses required to achieve neuromuscular block.

**Nicotinic blockers, e.g., *d*-tubocurarine.** Everett et al<sup>31</sup> reported that the *d*-tubocurarine molecule contains only one per-

manent quaternary nitrogen, whereas the other nitrogen is a tertiary amine with a pKa 8.1. *d*-Tubocurarine can release histamine and block ganglionic nicotinic transmission of both the vagus and sympathetic pathways within the neuromuscular-blocking dose range. Both the ganglion-blocking and the histamine-releasing properties of the drug may be attributed to the presence of a tertiary amine.

**Muscarinic blockers, e.g., pancuronium and gallamine.** The two drugs do not release histamine or block ganglionic transmission. However, both block the vagal muscarinic receptors in the dose range required for neuromuscular block. The vagolytic properties of gallamine overlie the neuromuscular blocking action,<sup>26</sup> and is dose-related<sup>32</sup>; that of pancuronium is only significant at the upper end of the neuromuscular dose-response curve.<sup>26</sup> The potent vagolytic effect of pancuronium and gallamine may be related to their structure. Pancuronium is the nondepolarizing relaxant most closely related structurally to acetylcholine, whereas the vagolytic property of gallamine is due to the presence of three positively charged nitrogen atoms.<sup>30</sup>

The antivagal effects of both gallamine and pancuronium are limited to the cardiac muscarinic receptors. Such selective vagolytic effect on the heart denotes that the muscarinic receptors of the heart, in analogy with the cardiac beta-adrenergic receptors, may be different from muscarinic receptors present elsewhere.<sup>33</sup>

In addition to the classic receptors that mediate the autonomic responses, specific receptors are present presynaptically that regulate the release of the transmitter. At the autonomic ganglia, transmission is modulated by a cholinergic muscarinic monosynaptic excit-

atory pathway and a multisynaptic inhibitory pathway. The latter contains an interneuron possessing a muscarinic receptor, which upon stimulation causes a release of inhibitory neurohumor, possibly dopamine.<sup>34</sup> At the sympathetic nerve terminals, presynaptic alpha adrenergic receptors ( $\alpha_2$ ) mediate a negative feedback mechanism that leads to inhibition of catecholamine release probably by restricting the calcium available for the excitation-secretion coupling. In contrast, presynaptic beta-adrenoreceptors ( $B_3$ ) mediate a positive feed-back mechanism leading to an increase in transmitter release; this mechanism appears to be mediated through an increase in the levels of cyclic adenosine monophosphate in the adrenergic nerve endings. In addition to the alpha- and beta-presynaptic adrenergic receptors, inhibitory muscarinic receptors and excitatory nicotinic receptors have been described.<sup>35</sup>

Muscle relaxants that have nicotinic or muscarinic-blocking action can, therefore, modulate sympathetic transmission and catecholamine release. Pancuronium and gallamine can inhibit the inhibitory muscarinic receptors at the sympathetic ganglia and the adrenergic postganglionic nerve terminals and thus increase the release of catecholamines.<sup>34, 36, 37</sup> In contrast, *d*-tubocurarine might block the excitatory nicotinic receptors reducing catecholamine released by the nerve terminals.<sup>38</sup>

The main hemodynamic effects of muscle relaxants can be attributed to their autonomic effects.<sup>39-41</sup> Drugs with minimal autonomic side effects such as metocurine and alcuronium produce the least hemodynamic changes. In contrast, nicotinic blockers such as *d*-tubocurarine will diminish the systemic vascular resistance and lower cardiac output and blood pressure, whereas

muscarinic blockers such as gallamine and pancuronium will increase myocardial contractility and arteriovenous conduction,<sup>42</sup> and induce tachycardia and hypertension.

The hemodynamic effect of muscle relaxants, and the interaction with the anesthetic used, drug therapy, and the condition of the patient, are factors that determine the choice of the relaxant. For example, neuromuscular blocking drugs having a nicotinic blocking effect, such as *d*-tubocurarine, may be the relaxants of choice in hypertensive patients or whenever a hypotensive technique is planned. In contrast, pancuronium may be selected in shocked and hypovolemic patients. Hypotension should be avoided in patients with coronary artery disease, low fixed cardiac output, and those with intracardiac shunts. Hypertension should be avoided in patients with coronary artery disease, aortic insufficiency, and mitral insufficiency. Tachycardia should be avoided in patients with coronary artery disease, aortic and mitral stenosis, and in any patient with small ventricular stroke volume. Anesthesiologists should choose the relaxant that best produces the desired cardiovascular effects on the individual patient.<sup>43</sup>

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