Adverse Effects of Nondepolarising Neuromuscular Blocking Agents
Incidence, Prevention and Management

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Summary
Nondepolarising muscle relaxants block neuromuscular transmission, acting as antagonists of the nicotinic receptors at the neuromuscular junction. Their undesired effects are frequently caused by interaction with acetylcholine receptors outside this junction, and autonomic cardiovascular effects may result. Other adverse effects include anaphylactic or anaphylactoid reactions, and histamine release. Various disease states may present specific considerations in the use of nondepolarising muscle relaxants. Although many complications of these drugs (such as prolonged block or resistance) are easily treated, others may necessitate immediate intervention and vigorous therapy. Careful selection of an appropriate relaxant for a particular patient will usually prevent the occurrence of complications.
Neuromuscular blocking drugs are designed to structurally resemble acetylcholine. This allows them to interact with the cholinergic site on the nicotinic receptors at the neuromuscular junction. The bulky nature of nondepolarising muscle relaxants (NDMR) molecules, compared with that of acetylcholine, causes these drugs to interact with the receptors as antagonists, rather than agonists.

NDMRs are divided according to basic molecular structure into steroidal and nonsteroidal agents. Nonsteroidal agents include benzylisoquinolinium and nonbenzylisoquinolinium compounds. Each class is associated with its own particular complications, and some complications are common to more than one class. For example, Benzylisoquinolinium agents are associated with histamine release, whereas steroidal muscle relaxants are not. Autonomic adverse effects, anaphylactic and anaphylactoid reactions are common to all classes of muscle relaxants. Adverse effects may affect neuromuscular sites or other organ systems. This review discusses complications associated with NDMRs. For a review of adverse effects associated with depolarising neuromuscular blocking agents, see Book et al. (1994).

1. Cardiovascular Effects

NDMRs exert cardiovascular adverse effects via the autonomic nervous system or via histamine release. Autonomic mechanisms may be further subdivided into muscarinic and nicotinic effects. Structure-activity relationships exist in determining adverse effects of muscle relaxants. Benzylisoquinolinium relaxants may cause histamine release, whereas steroidal relaxants are rarely associated with histamine release. Autonomic mechanisms are common to both steroidal and benzylisoquinolinium nondepolarising relaxants.

Most cardiovascular adverse effects are well tolerated by most patients. Caution should be taken in administering some muscle relaxants to certain patients. For example, drugs which cause tachycardia may not be appropriate for a patient with coronary artery disease. Adverse effects may also be used to advantage. Thus, vagotonic drugs (i.e. sufentanil) may be combined with drugs which cause tachycardia.

1.1 Autonomic Mechanisms

Cholinergic receptor sites exist throughout both the sympathetic and parasympathetic autonomic nervous system, and are classified into muscarinic and nicotinic subtypes. All muscarinic receptors are stimulated by muscarine and inhibited by atropine (Weiner & Tayler 1985). Muscarinic receptors are, nevertheless, heterogeneous and are classified into 3 subtypes called M₁, M₂ and M₃ (Scott 1992; Vizi et al. 1989) [fig.1]. They exist both presynaptically and postsynaptically. Presynaptic muscarinic receptors mediate the release of neurotransmitters, including noradrenaline. They also inhibit the release of noradrenaline from sympathetic nerve terminals (Vizi et al. 1989).

Postsynaptic muscarinic receptors exist on effector cells, including atrial and nodal cells of the heart, smooth muscle of arterioles and gastrointestinal tract, the eye, and neuronal cell bodies (Vizi et al 1989). Because muscarinic receptors are heterogeneous, NDMRs with low muscarinic safety ratios do not manifest muscarinically-mediated adverse effects uniformly at all muscarinic sites. Block of muscarinic sites by NDMRs may cause tachycardia via a vagolytic effect, by release of nor-