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Haemodynamic reactions to succinylcholine - an alternative hypothesis

To the Editor:

I read with great interest the elegant hypothesis proposed by Nigrovic concerning the mechanisms of adverse reactions to succinylcholine (SCh).¹ The hypothesis postulates that SCh modulates norepinephrine (NE) release from the sympathetic nerve terminals by acting on the presynaptic nicotinic (N) and muscarinic (M) cholinergic receptors. Activation of the N receptors increases the release of NE, while activation of the M receptors attenuates the release. Due to the mutually opposing effects, the net response to SCh is small, variable, and of little clinical significance. The initial activation is followed by a period of desensitization. However, desensitization of the N receptors may outlast that of the M receptors leading to an unbalanced response which can result in adverse haemodynamic reactions.

Our alternative hypothesis attributes the adverse cardiovascular effects of SCh to its postsynaptic muscarinic action on the sinoatrial node (SAN), which is modulated by its nicotinic action on both the vagal and sympathetic systems.

Succinylcholine, consisting as it does of two acetylcholine molecules linked together, appears to display all the stimulant actions which acetylcholine can exercise on both the N and M cholinergic receptors.² Goat has confirmed the direct acetylcholine-like action of SCh on the isolated heart.³ This effect is a muscarinic response and can be blocked by atropine. The direct effect of SCh on the postsynaptic muscarinic receptors around the SAN can be modulated by the sympathetic and vagal balance controlling the SAN. Succinylcholine can activate the nicotinic cholinergic receptors responsible for transmission through vagal ganglia, and hence

potentiates the direct muscarinic effect of SCh on the SAN. However, SCh, similar to other nicotinic agonists can also stimulate the ganglionic sympathetic cells, as well as the nicotinic receptors on the postganglionic sympathetic terminals,⁴ resulting in release of NE,^{4,5} which can counteract the vagotonic and direct muscarinic effect of SCh, and may even result in tachycardia and hypertension. This release following the initial bolus of nicotinic agonists may transiently deplete the stores of NE, and hence repeating the injection of SCh within a certain period may not release NE in a concentration that can counteract its vagotonic and direct muscarinic effects. This alternative hypothesis can explain the absence of bradycardia following a single bolus of SCh, and the frequent occurrence of bradycardia following repeated doses.

In contrast to the intermittent administration of SCh, no serious haemodynamic changes are usually associated with the continuous infusion of SCh in normal patients, or with a bolus injection in patients with the atypical pseudocholinesterase. The prolonged presence of SCh may produce an initial stimulation followed by gradual desensitization of both the nicotinic and muscarinic receptors, and hence may induce a mutually opposing effect on the sympathetic and the vagal control of the heart.

In conclusion, it appears that the direct postsynaptic muscarinic action of SCh on the SAN is modulated by its nicotinic effect on the cardiac vagal/sympathetic balance. Whenever the cardiac vagal tone predominates, the injection of SCh can produce bradycardia and hypotension. In contrast, whenever the sympathetic tone predominates, SCh can produce tachycardia and hypertension.

Nigrovic suggested in his hypothesis that "clinical situations most frequently associated with early haemodynamic crises after the administration of SCh share an altered state of the sympathetic nervous system as their common denominator".¹ However, these haemodynamic crises can also occur secondary to an abnormal neuromuscular response to SCh, such as malignant hyperthermia, or excessive K⁺ release from denervated muscles.

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REPLY

I thank Dr. Baraka for his kind letter commenting on the hypothesis concerning the mechanism of the early adverse haemodynamic reactions to succinylcholine (SCh) and for offering an alternative hypothesis.

In general, Dr. Baraka concurs with the essential points of the hypothesis. The reason he perceived the need for supplemental suppositions may be attributed to an incomplete consideration of the hypothesis. In his rendition of the original hypothesis, Dr. Baraka emphasizes one aspect of the hypothesis (*viz.*, the modulation of the release of norepinephrine via the interaction of SCh with the presynaptic cholinergic receptors on the sympathetic terminals) to the detriment of the other (*viz.*, the interaction of SCh with the postsynaptic cholinergic receptors). The neglected part is subsequently introduced as an alternative hypothesis.

First, the action of SCh on the sino-atrial node is, in fact, duly considered in the hypothesis. The notion that SCh can activate the (postsynaptic) muscarinic receptors at this site and cause bradycardia is indeed an old one. Our hypothesis goes beyond this fact. In its essence, it offers an integral picture of the pharmacologic actions of SCh at the level of the autonomic receptors. Based on these considerations, expected responses at the level of the whole organism are derived and the correlations with clinical reports outlined. The notion is proffered that these autonomic responses (both the pre-existing and the pharmacologically induced ones) in conjunction with hyperkalaemia determine the extent and the character of the SCh-induced haemodynamic crises.

In the context of the hypothesis "... the mutually opposing effects resulting from the activation of these cholinergic receptors by succinylcholine ..." refers to all

cholinergic receptors (both pre- and postsynaptic, muscarinic and nicotinic) and not just to presynaptic cholinergic receptors on the postganglionic sympathetic terminals. Certainly, were the whole hypothesis restricted to these only - as interpreted by Dr. Baraka - there would indeed be a need for additional postulates. The hypothesis, however, as originally presented does incorporate these ideas.

The second point put forward by Dr. Baraka is the suggestion that SCh activates the cholinergic receptors in the autonomic (sympathetic and parasympathetic) ganglionic cells. Although this notion has been entertained frequently in the past, the following critical point has not been considered: interaction of SCh with the cholinergic receptors on the ganglionic cells would produce not only an initial activation but also a subsequent inactivation of these receptors. During the inactivation phase all autonomic reflexes would be abolished for as long as SCh is present (receptors maintained chemosensitive). However, neither the infusion of SCh nor the decreased degradation rate of SCh in patients with abnormal pseudocholinesterase have been reported to produce the clinical picture of an autonomic (sympathetic and parasympathetic) areflexia. In addition, the data documenting the release of norepinephrine - as cited by Dr. Baraka - are easily and adequately explained by postulating only an activation of the presynaptic nicotinic receptors on the postganglionic sympathetic terminals. Thus, I believe that the notion of a clinically important interaction of SCh with cholinergic receptors in the autonomic ganglia, although perhaps possible, is not likely.

The third point of Dr. Baraka's alternative hypothesis is the suggestion that SCh might lead to a depletion of norepinephrine (NE) stores in the sympathetic terminals. This interesting suggestion is not supported by the available pharmacologic and clinical information. First, even under the most extreme experimental conditions, depletion of NE stores requires relatively prolonged treatment with suitable agents. Repletion is also a prolonged process. Second, the sudden massive release of NE to the extent of depletion of the NE stores would be expected to produce a haemodynamic crisis. This is clearly not the case after the customary intravenous bolus administration of SCh. Moreover, the depletion of NE stores on the sympathetic terminals would not account for other clinical observations (*e.g.*, a critical time interval between the first and the second injection of SCh, the more frequent occurrence of bradycardia in infants, etc.). Our hypothesis also offered pharmacologic interpretation for clinical observations after the slow infusion of SCh or after the intramuscular administration. Thus, I do believe that SCh may lead to a fractional release of NE from the stores at the sympathetic terminals. I doubt that a depletion of the stores is likely.

Lastly, Dr. Baraka comments on SCh-induced hyperkalaemia and malignant hyperpyrexia. The relationship between increased concentrations of potassium in the extracellular fluid, catecholamines, and the anesthetic agents is complex. According to our hypothesis, hyperkalaemia is only one event in the sequence of events leading