

tronic instrument has the further advantage that it will function as a breathing circuit disconnection alarm and as a respiratory rate meter throughout the operation. The instrument is also useful as an apnea alarm for nonintubated patients during sedation with regional block, for recovery from anesthesia, or when epidural or intrathecal narcotics are employed.

We keep one of these devices attached to the anesthesia machine in our cesarean section room and have found it entirely satisfactory for verifying proper intubation. We keep another unit in the operating suite to supplement our (more slowly responding) time-shared mass spectrometer system during difficult intubations, and we have a third unit to verify all intubations performed in the intensive care unit. The portability of

the instrument would make it appear to be useful in emergency rooms and ambulances as well.

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Concerning the Site of Action of Verapamil on Skeletal Muscle

To the Editor:—I read with great interest the report of Durant *et al.*¹ on the potentiation of the neuromuscular (NM) blocking effect of pancuronium and succinylcholine by verapamil in the rabbit. I would like to take issue, however, with their statement that “the action of verapamil is not centered on the muscle fiber itself.” They based their conclusion on two observations, both of which appear to be irrelevant: The first of these, the observation that under the experimental conditions described, verapamil alone had no effect on the indirectly elicited twitch in the rabbit does not give any information on the site of action of verapamil. It only indicates that, because the sensitivity of the cardiovascular system to verapamil is greater than that of skeletal muscles, it was impossible to use high enough doses to inhibit twitch development. In *in vitro* experiments, in the absence of cardiovascular effects, twitch could be inhibited completely by verapamil.² It was also possible to moderately inhibit tension development *in vivo* by the infusion of 0.4 mg/kg verapamil over a 10-min period in the tibialis anterior muscle of rats, indirectly stimulated by 0.1 s trains of 50 Hz supramaximal impulses of 0.2 ms duration, every 20 s.³

Their second observation, referring to good correlation between the electromechanogram and the electromyogram (EMG) is also irrelevant to the site of action of verapamil. Both the twitch and the EMG represent the end result of a long chain of events. Interruption of this chain at any one or more levels (*e.g.*, motor nerve terminal, cholinergic receptors or ionophores of the postjunctional membrane, sarcolemma) by verapamil would cause similar decrease of the twitch and the amplitude of the EMG. About the only situation when there can be a

significant difference between the EMG and the twitch is when the intracellular utilization of Ca^{2+} , essential for the formation of the contractile actomyosin complex, is prevented by a compound such as dantrolene.

In contradistinction to the assumption that the site of the inhibitory effect of verapamil is the NM junction there is considerable evidence indicating that verapamil acts primarily at the sarcolemma or the sarcoplasmic reticulum membrane. The finding that *in vitro* the ED₅₀ of verapamil was lower (26.3 μ M) during direct than during indirect (37.7 μ M) stimulation² supports this alternative hypothesis. If the primary site of the inhibitory effect of verapamil would be the NM junction, twitch tension should be inhibited more during indirect than direct stimulation. Furthermore, during indirect stimulation, inhibitory concentrations of verapamil at first increase tension development. Clarification of the mechanism of the initial stimulating effect and the primary site of action of verapamil will have to await the outcome of neurophysiologic studies. At the present time, however, most of the evidence favors a postsynaptic site of action for verapamil.

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In reply:—We thank Dr. Foldes for his interest in our article.¹

Dr. Foldes takes issue with our statement “the action of verapamil is not centered on the muscle fiber itself” on two grounds, namely: 1) that we did not use a high enough dose of verapamil alone to see an effect; 2) that a good correlation between the indirectly elicited twitch tension and electromyogram (EMG) does not exclude an action of verapamil directly on the muscle fiber.

We most strongly disagree with these two points raised by Dr. Foldes for the following reasons:

Surely one could raise the same objection as described above in the first point to any study demonstrating the absence of effect of a drug? We should point out that the highest dose of verapamil that we used (1 mg/kg) is higher than that used by Dr. Foldes in his own *in vivo* studies² (0.4 mg/kg) and as described in his letter. In addition, the concentrations which Dr. Foldes describes, in his letter, as having used on the isolated rat hemidiaphragm preparation are extremely high (26.3 and 37.7 mM). Our study was intended to have some clinical relevance, and there seemed little point in using a dose of verapamil greater than 1 mg/kg, since the usual clinical dose is approximately 0.1 mg/kg.

We believe that the second point is not irrelevant to our hypothesis. The EMG is not as near the end of “a long chain of events” as is the twitch response, and if verapamil were having any effect on the muscle fiber contractile process (beyond the electrophysiologic events) then dissociation of the EMG and twitch response definitely would result. However, we do not exclude an action of verapamil on the motor nerve terminal, cholinergic receptors, or ionophores of the postjunctional membrane, which, incidentally, we consider to be integral to the neuromuscular junction.

Furthermore and relevant to the objections raised by Dr. Foldes, we have carried out an additional study in rabbits anesthetized with halothane utilizing the same protocol as described in our study¹ with one difference. Instead of eliciting twitch responses of the gastrocnemius muscle with indirect stimulation, we applied direct stimulation via needle electrodes using square-wave stimuli of 1-ms duration at a frequency of 0.1 Hz and supra-maximal voltage.³ When neuromuscular transmission was eliminated with a large dose (1 mg/kg) of vecuronium, we observed absolutely no effect of verapamil on

the directly elicited twitch tension in the dose range 0.01 to 1.0 mg/kg. This evidence supports our original hypothesis that the action of verapamil is not centered on the muscle fiber itself. Further support for this hypothesis is provided by the observation in our article¹ that the neuromuscular block produced by alpha-bungarotoxin was unaffected by verapamil. If verapamil were having an effect on the muscle fiber directly, then the neuromuscular block produced by pancuronium, succinylcholine, and alpha-bungarotoxin would be potentiated in a similar manner. We found that the neuromuscular blockade produced by alpha-bungarotoxin was unaffected by verapamil.¹

While we do not question the findings of Dr. Foldes' study described in his letter, we do question whether his results are conclusive evidence for an action of verapamil solely at the sarcolemma or sarcoplasmic reticulum. Additionally, the pulse duration of the stimulus used for direct stimulation, 0.2-ms described by Dr. Foldes and his colleagues in their abstract,⁴ is extremely unlikely to result in recruitment of all the muscle fibers and consequently gives a result that is very difficult, if not impossible, to interpret.

Thus, we stand by our original hypothesis that the potentiating effect of verapamil on the neuromuscular block produced by pancuronium or succinylcholine in our study is due to a neuromuscular effect of verapamil. However, we agree that further studies are necessary to clarify whether this effect at the neuromuscular junction is either prejunctional or postjunctional.

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