

CORRESPONDENCE

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In Reply:—Thank you for the opportunity to comment on the remarks made by Drs. Wappler and Fiege regarding our case report. We agree that the clinical course of malignant hyperthermia (MH) is variable and that postoperative rhabdomyolysis can be the only symptom of MH.

In response to the questions posed by Drs. Wappler and Fiege, our patient had no history of anesthesia induction, and neither he nor his family members had a history of muscle diseases or anesthetic problems. Except for an increase of creatine kinase (CK) up to 13,409 IU/l, he did not show signs of MH perioperatively (e.g., muscle rigidity, metabolic acidosis, hypercapnia, tachycardia, or fever). The results of arterial blood gas analysis did not show abnormal findings during or after the operative procedure. Other pathologic findings included thoracolumbar paravertebral muscle necrosis, which was confirmed by computed tomography, and ischemic dermal damage on the back. Immediately after emerging from the anesthesia, the patient reported severe back pain. At the involved area, pneumatic support was placed in the hyperlordotic supine position for 11 h; therefore, the cause of elevated CK is due to the ischemic damage by the enforced hyperlordotic position.

According to the Clinical Grading Scale,¹ our patient had a raw score of 15 (i.e., CK elevation), but this scale should be estimated within 24 h after the administration of an anesthetic. The CK level 24 h later was 3,544 IU/l, and increased to a maximum of 13,409 IU/l at 30 h. These data suggest that our patient did not have MH. Further, review of the literature revealed that CK levels after intraoperative-pressure muscle ischemia are lower (< 75,000 U/l),² which is compatible with our data. Our patient's preoperative CK level of 168 IU/l was within the normal range (20–180 IU/l) seen in our hospital. Thirty days later, this patient underwent a second operation for closure of the jejunostomy, which

proceeded uneventfully using the same method and agents of anesthesia as in the first operation.

We still conclude that rhabdomyolysis was induced by the pneumatic device, not by MH.

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Analgesic Effects of Neostigmine in the Periphery

To the Editor:—In recent years, the journal *ANESTHESIOLOGY* has published several reports on the analgesic effectiveness of the cholinesterase inhibitor neostigmine. Although there is good evidence for a spinal action of neostigmine,^{1,2} a rationale for a peripheral mechanism of action is lacking. Intrathecal injection of neostigmine produces analgesic effects in animals,³ including humans,⁴ accompanied by a high incidence of side effects. The inhibition of spinal cholinesterase

results in an increase of endogenous acetylcholine, which is most likely released from intrinsic cholinergic neurons within the dorsal horn of the spinal cord.⁵ These cholinergic neurons terminate in the vicinity of primary afferents,⁵ which express muscarinic receptors.^{6,7} Consistently, analgesic effects of intrathecal neostigmine could be reversed by muscarinic receptor antagonists.⁸ The analgesic effect may be explained by a muscarinic presynaptic inhibition of glutamatergic

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afferents, similar to how it has been described in the neostriatum.⁹ An important prerequisite for the effectiveness of neostigmine is a tonic cholinergic activity.^{10,11}

Although these mechanisms are clearly described for the spinal cord, evidence is lacking for the periphery. Therefore, the negative result of adding neostigmine to a mepivacaine axillary plexus block in the study by Bouaziz *et al.*¹² is not surprising. How would neostigmine exert an effect within the nerve sheath of the axillary plexus? An endogenous release of acetylcholine does not exist. Interestingly, the authors hypothesized a peripheral action of neostigmine based on the demonstration of peripheral muscarinic receptors only⁶; however, this is not enough. In their discussion, they refer to studies that investigated the effects of muscarinic agonists in spinal cord slice preparations *in vitro*¹³ or intrathecally *in vivo*.¹⁴ However, these effects are not described for peripheral nerve endings, and neostigmine should not be confused with muscarinic agonists. Therefore, a lack of neostigmine effectiveness within the nerve sheath of the axillary plexus should have been anticipated. For the same reasons, the results of experimental¹⁵ and clinical¹⁶ studies that showed analgesic effectiveness of intra-articular neostigmine are surprising. In rats, the intraarticular injection of neostigmine produces moderate analgesia to thermal stimuli,¹⁵ which is allegedly reversible by intraarticular atropine, although data were not shown in that study. In patients undergoing arthroscopic meniscus repair, intraarticular injection of 500 mg neostigmine resulted in a significant difference in pain intensity at 1 h postoperatively, in total consumption of intravenous rescue analgesics, and in time to first analgesic use.¹⁶ To support their hypothesis of a peripheral site of action, the authors refer to "preclinical data suggesting peripheral antinociceptive effects of acetylcholine."¹⁷ However, acetylcholine is an agonist at muscarinic receptors. Again, the cholinesterase inhibitor neostigmine should not be confused with muscarinic agonists. In both cases, the question arises: Which cells in the periphery are responsible for a tonic cholinergic activity? This question has not been addressed in either of these studies; therefore, the mechanism of action of peripherally applied neostigmine is still lacking, and the identification of the presumed source of peripheral acetylcholine is urgently needed.

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