Specific Therapies of Biguanide-induced Lactic Acidosis

To the Editor.—Mercker et al. reported a case of severe biguanide-induced lactic acidosis. However, the authors did not discuss specific therapies. In such case, the administration of sodium dichloroacetate (DCA) should have been considered. DCA is an antidiabetic agent that activates the pyruvate dehydrogenase complex, the mitochondrial enzyme that catalyzes the conversion of pyruvate to acetyl-coenzyme A and carbon dioxide. In dogs DCA has been reported to correct lactic acidosis induced by phenformin, another biguanide that induces lactic acidosis more commonly. In the patient described, an ongoing infection could have contributed to the overproduction of lactate. Even in endotoxin-induced lactic acidosis, DCA administration has been shown to reduce blood lactate levels. Administration of DCA could reduce plasma lactate levels in patients with lactic acidosis caused by various etiologies, even though in a large clinical trial, such intervention did not improve survival rates.

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In Reply.—We appreciate the interest and comments of our colleagues regarding our case report and would like to thank the editorial board for the opportunity to respond.

We agree with Lustik et al. that a patient’s diabetes mellitus should be under good control perioperatively. Therefore, we would not stop metformin administration without starting an alternative therapy if appropriate.

Nevertheless, we are much more concerned about perioperative metformin medication than Lustik et al. are. The patient mentioned in our case report was treated according to the recommendations suggested by Lustik et al. He presented no contraindications for metformin (except low caloric input) until he developed severe lactic acidosis. Therefore, stopping metformin could prevent a rare, but significant, risk for the patient, whereas the potential benefits of continuing the drug are rather vague.

According to the new manufacturer’s recommendations in Germany, metformin should be omitted 2 days before and after general anesthesia. The risk to develop perioperative problems that would
represent a contraindication for metformin medication (insufficiency of cardiovascular, pulmonary, or renal function; infections; catabolic metabolism) does not differ significantly if operations of the same size are performed in regional anesthesia. In case of ambulatory surgery we have concerns, and the development of contraindications might proceed unnoticed.

Although we agree with Lustik et al. regarding the importance of good diabetic control, we prefer to continue our rather restrictive practice of perioperative metformin therapy.

Sodium dichloracetate (DCA), as proposed by Preiser and Vincent, could be an interesting future option for the therapy of lactic acidosis, especially because it could provide more than just symptomatic therapy.

However, DCA does not belong to the standard therapy of biguanide-induced lactic acidosis. Further, the clinical trials Preiser and Vincent refer to do not suggest DCA to be a magic bullet. Because metformin-induced lactic acidosis is a rare phenomenon and our personal experience is limited, we did not consider a therapy besides the recommended standards in this case.

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Implementation of Pharmaceutical Practice Guidelines—Once Again

To the Editor—In a recent Letter to the Editor1 in response to an article by Lubarsky et al.2 I pointed out that anesthetic agents and muscle relaxants may have a significant effect that lasts beyond the PACU period, and therefore an investigation of the effect of practice guidelines on clinical outcome and cost–benefit analyses should include the period after the patients are discharged to the ward. I referred to our recent prospective, randomized, controlled study of postoperative pulmonary complications (POPC) after the use of pancuronium, atracurium, and vecuronium in nearly 700 patients.3,4 We found that not only was the incidence and the degree of residual block in the PACU significantly increased in the pancuronium group, but also significantly more patients in this group developed POPC in the ward (16.9%) compared with the two other groups (5.4%).

In Dr. Lubarsky’s response, he argued that the practice guidelines he proposed regarding the use of pancuronium are sound as long as enough medication is administered to achieve appropriate reversal, and that reversal should be monitored by standard train-of-four monitoring, making sure a twitch is present before reversal, and one should assess the ability to sustain tendon for 5 s in addition to having 4/4 twitches of near equal magnitude (≥70 % twitch).5,6

The problem is that during routine anesthesia given by anesthetists without any special interest in neuromuscular blocking agents, residual neuromuscular block after long-acting neuromuscular blocking agents is not eliminated using routine clinical tests and tacile or visual evaluation of the response to train-of-four or tetanic stimulation as described by Lubarsky.5,6 It was demonstrated manually or visually to judge the degree of train-of-four or tetanic fade (50 Hz) with sufficient certainty to exclude residual block.8-10 (Viby-Mogensen et al., unpublished observation). In studies claiming the opposite, the anesthetists evaluating the response to train-of-four nerve stimulation were dedicated and experienced observers.11,12 To exclude clinically significant residual neuromuscular block after the use of the long-acting neuromuscular blocking agents during routine anesthesia, more objective methods of monitoring such as electromyography, accelerometry, or possibly double burst stimulation must be applied.13,14

Dr. Lubarsky claims that our patients received an inadequate dosage of neostigmine. It may or may not be so in some cases, although this is not the issue. The issue is that the anesthetists in our study were instructed to do their best to avoid residual neuromuscular block. They were instructed to aim at a level of neuromuscular block during surgery corresponding to one or two responses after train-of-four stimulation, as proposed by Lubarsky et al. A minimum of two responses was required to be present before initiation of reversal. Reversal was induced with neostigmine, 2.5 mg, but supplementary doses of neostigmine, 1.25 mg, could be given up to a total of 5 mg, if judged necessary by the anesthetists. Tracheal extubation was performed when four equal responses were felt after train-of-four stimulation and when clinically sufficient respiration was judged to be present. So once again it was documented that during routine anesthesia, clinical evaluation with manual evaluation of the train-of-four response does not exclude residual neuromuscular block after pancuronium.

On the basis of the previous, it is difficult for me to accept the conclusion of Lubarsky et al.: the routine use of the long-acting agent pancuronium did not adversely influence outcome. Lubarsky et al. have not convincingly documented by objective methods that their patients did not have residual neuromuscular block in the recovery.