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Neuroprotective and Antiepileptic Activities of Ketamine in Nerve Agent Poisoning

To the Editor:—We read with interest the review by Ben Abraham *et al.* providing guidelines for the care of victims of bioterrorism, in the October issue of ANESTHESIOLOGY.[1] This article is an important contribution at a time when using a nerve agent such as sarin, even in the civilian context, is increasingly likely.[2]

The authors stress the possibility of dangerous reactions occurring when ketamine is used in sulfur mustard casualties. However, this assessment based on unexplained results would require further investigations.[3] Despite this word of caution, we would like to emphasize the benefits of ketamine for nerve agent poisoning.

Ketamine has been safely used for more than 35 yr but was gradually banished from usual practice because of psychedelic side effects and was supplanted by new, easier to handle drugs. However, the potential neuroprotective effects linked to the blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors prompted a renewed interest in phencyclidine derivatives such as ketamine[4] and led to the discussion of one of the major contraindications of the molecule: brain damage.

Because of cardiovascular and respiratory favorable properties, ketamine seems to be an anesthetic of choice for military surgery.[5] Better oxygen delivery and survival after ketamine anesthesia have been reported in experimental models of hemorrhage.[6] Reduced respiratory depression with higher Pa_{O_2} values, when compared to halothane, makes it particularly safe for analgesia during surgical procedures far from the operating room.[7] During combat in a chemical warfare environment, the IV route would be difficult to consider and administration of ketamine by the intramuscular route would clearly be an advantage.

Of particular interest is the ketamine induced NMDA receptor-channel noncompetitive blocking, which most probably explains its neuroprotective and anticonvulsant properties. This makes ketamine particularly suitable for induction and maintenance of anesthesia in patients exposed to organophosphorous compounds.[8] Although ketamine has occasionally been reported to induce seizures, a larger body of evidence suggests that it actually displays anticonvulsant and neuroprotective properties.[9]

Not only the accumulation of acetylcholine but also excitatory amino acid neurotransmission is responsible for the nerve agent-induced *status epilepticus* and brain damage.[10] NMDA receptors, which are largely permeable to calcium, are particularly involved. A voltage-dependant magnesium block characterizes the NMDA channel. Depolarization, the final common pathway of multiple neuronal injuries, causes the magnesium block to be lifted, enabling calcium to enter the cell and induce the cascade of neuronal damage. Ketamine or Dizocilpine (MK-801) are noncompetitive antagonists that act inside the canal, at the phencyclidine site and demonstrate use-dependent, open-channel blockade. The first experimental results obtained with NMDA receptor antagonists in soman-poisoned animals demonstrate that only the animals with *status epilepticus* exhibit neuronal damage, and the longer the convulsions, the worst the neurologic outcome. Limitation of seizures with these antagonists may thus prevent definite neurologic damage.[11] Because of an increasing difficulty in stopping nerve agents induced on-going seizures with time, it would be necessary to consider the use of ketamine as early as possible and multiple injections of anesthetic doses. The S(+) isomer, which is two to four times more potent than the R(−) isomer because of a superior pharmacological action on NMDA receptors, may exhibit better neuroprotective properties, although definitive results are still expected.[12]

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David C. Warltier, M.D., Ph.D., handled this exchange as Editor of the Review Article.

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In Reply:—We read with interest the letter of Mion *et al.* regarding our review article. The issue that the authors raise, *i.e.*, our report of experimental data indicating a potential dangerous reaction to ketamine (prolonged apnea and respiratory distress) when animals were exposed to sulfur mustard, is theoretical, at least in part. As reviewers, we could do no more than collect and present the specific experimental model and the related results at face value. The clinical aspects of the possible use of ketamine in nonconventionally intoxicated patients is problematic on several fronts. First, because ketamine potentially generates undesirable side effects *per se* that additively affect target-

organs of nerve agents (*e.g.*, central nervous system: hallucinations; respiratory system: increased secretions), such potentiation may lead to unacceptable neurologic conditions. Second, ketamine has never been accepted clinically as a safe drug to control epileptic episodes, although its potential has been shown in animal models. Indeed, Mion *et al.*'s use of the word "may" is entirely appropriate in illustrating a potential but not contemporary use of ketamine as an antiseizure drug because of its NMDA-antagonistic properties. In the clinical setting, following the American, Israeli, and European protocols of antinerve agent protection, however, benzodiazepines are the *only* proven drugs to effectively control seizures while scopolamine, another weak NMDA-receptor antagonist, is the drug used to antagonize organophosphates' central effects. We indeed discussed in our review article the notion brought up by Mion *et al.* that ". . . ketamine [is] suitable for induction and maintenance of anesthesia in patients exposed to organophosphorous compounds."[1] Importantly, this reference used by the authors is inappropriate and extrapolative, because the article by Sheth *et al.* dealt with neither anesthesia nor organophosphorous compounds.

Finally, the concise explanation of the NMDA receptors-ketamine interactions in the central nervous system was appropriate, considering the scope of our review.

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Possible Dangers of Discontinuing Statins Perioperatively

To the Editor:—I recently read with great interest the case report by Forestier *et al.*[1] "Severe Rhabdomyolysis after Laparoscopic Surgery for Adenocarcinoma of the Rectum in Two Patients Treated with Statins." With the rapidly increasing number of patients taking HMG Co-A reductase inhibitors (statins) for treatment of lipid disorders, I concur with the authors that peri-operative rhabdomyolysis might become a significant problem.

However, I would like to air a note of caution in regards to the authors final statement: "Considering that these drugs are used for long-term prevention, stopping the drug for a few weeks before surgery would not significantly decrease the cardiovascular protection." In the March issue of *Circulation*, Heeschen *et al.*[2] addressed this very topic in their study, "Withdrawal of statins increases event rates in patients with acute coronary syndromes." These authors investigated the effects of statin therapy in 1616 patients who had coronary artery disease and acute chest pain. They found that the patients who had their statin therapy discontinued on hospital admission for whatever reason actually did worse than the group who continued to receive their statins. The increased event rate was independent of cholesterol levels, and the only predictors of patient outcome were in fact troponin T elevation, electrocardiographic wave changes, and continuation of statin therapy.

With this study in mind, I would argue against Forestier's recommendation that statin therapy be withdrawn for a few weeks before surgery. This topic obviously needs more investigation before any recommendations can be made. The incidence of perioperative myopathy and rhabdomyolysis needs to be ascertained by a review with a larger cohort than 2. The next question raised then is: What is the incidence of rhabdomyolysis for the individual drugs within the statin class? Also, these patients taking the statins are at least at a mildly increased risk of perioperative cardiac events and potentially are at a major risk if in fact they have a lipid disorder and known coronary artery disease. Discontinuing the statins in these high-risk patients might actually be a major disservice to them if in fact they suffer a perioperative ischemic event and are without their statin therapy. The risk of rhabdomyolysis in patients on statins who have no known coronary disease might outweigh the risk of discontinuing the statins. When does the risk of perioperative rhabdomyolysis decrease—immediately postoperatively or days to weeks later, and when should the statin be restarted? These are all questions that must be answered before any recommendations regarding continuation/discontinuation of statin therapy in the perioperative setting can be firmly issued.

I would like to thank Forrestier *et al.* for raising this issue and for warning us about the risks of this increasingly popular class of drugs.

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In Reply:—Dr. Kreisler's comment concerning the risk of statin withdrawal is thought provoking. However, the study referred to concerns patients who were admitted for acute aggravated angina or acute coronary syndromes. These are patients with severe coronary heart disease, who may not be representative of the vast majority of statin users undergoing elective surgery in the absence of an acute coronary syndrome. If indeed stopping statins causes patients to run a risk of a serious coronary event, this is very worrisome, because most users are for primary prevention[1] without major coronary artery disease, and most stop the drug spontaneously within about 6 months. In that case, stopping (and therefore starting) statins may become a major factor in the risk of coronary events. Maybe it would be better in these patients not to stop, or alternatively not to start the drugs.

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