The case described by Cannon, Glazier, and Bauman in this issue is yet another that draws attention to a potentially important problem encountered with long-term use of high-dose propofol for sedation and control of intracranial pressure in both adult and pediatric head-injured patients. Propofol-infusion syndrome has been defined as the constellation of otherwise unexplained myocardial failure, metabolic acidosis, and rhabdomyolysis in the setting of prolonged high-dose propofol therapy. Hyperkalemia and renal failure have also been associated with this syndrome.

The patient described by Cannon and colleagues, an unfortunate 13-year-old girl who sustained a severe head injury, meets the criteria for propofol-infusion syndrome established by previous investigators. As with other cases, only an association between high-dose propofol and the syndrome has been shown. Nevertheless, the results of numerous reports and a recent dose analysis of propofol-infusion syndrome after long-term propofol therapy in adult head-injured patients, conducted by Cremer, et al., strongly suggest that the syndrome is, in part, related to propofol, even though a direct causal link has not been established. In the study by Cremer, et al., the syndrome developed in three (17%) of 18 adult patients receiving doses of 5 to 6 mg/kg/hr (83–100 µg/kg/min) and four (31%) of 13 patients receiving doses greater than 6 mg/kg/hr (> 100 µg/kg/min); all seven patients had received the drug for longer than 58 hours. This finding indicates that the syndrome is likely a multifactorial process; however, identification of predisposing factors for development of the syndrome remains elusive.

Recently, at the University of California at Los Angeles Medical Center, we treated at least one adult head-injured patient who experienced symptoms compatible with propofol-infusion syndrome who later died. Our patient had suffered a severe closed-head injury and subsequently experienced severe intracranial hypertension. Propofol was used initially for sedation and later at higher doses for an electroencephalographically defined burst suppression (mean dose 126 µg/kg/min, range 10–200 µg/kg/min; total duration of medication 55 hours). The development of metabolic acidosis, renal failure, and cardiovascular collapse in our patient evolved after propofol therapy was stopped. He died 9 days postinjury, 5 days after propofol therapy was ended. In our multicenter randomized trial of a 2% propofol formulation (from which data are still not available in the United States), we did not identify any patients who had propofol-infusion syndrome, although it is possible that it was not recognized at that time. Interestingly, in that study, the highest favorable outcome rate (70%), as assessed using the Glasgow Outcome Scale, was found in the group of 10 patients who received a high dose of propofol (average dose and duration 78 µg/kg/min and 128 hours, respectively).

In light of the recent report by Cremer, et al., and our own experience, we have curtailed our use of propofol. As suggested by Cremer, et al., and by Cannon and colleagues, until further data are available, prolonged high-dose propofol infusions (> 80–100 µg/kg/min for > 48–72 hours) should be administered with caution. It is probably prudent to monitor for early signs of the syndrome (for example, initial measurements of myoglobin and creatine kinase levels should be obtained within 24 hours after infusion begins) and to monitor the need for increasing inotropic support. If high-dose metabolic suppressive therapy is needed longer than 3 days, the alternative of pentobarbital may be considered; however, the potent cardiac depressant effects of this very long-acting agent should not be forgotten. Cardiovascular complications in many patients with severe head injuries who receive high-dose pentobarbital have been well documented over the last 20 years. Reversing these effects is difficult, given pentobarbital’s long half-life of 15 to 48 hours.1,3,5

Hopefully, reports such as those by Cannon and colleagues and Cremer, et al., will provide impetus for AstraZeneca to investigate carefully the cause(s) of, risk factors for, and possible solutions to propofol-infusion syndrome, and to continue to seek ways to improve on this otherwise useful short-acting sedative/anesthetic agent.
References


RESPONSE: We appreciate Dr. Kelly’s editorial regarding our case report and his discussion of the recent article in Lancet by Cremer, et al.¹ Our case report is yet another example of propofol-infusion syndrome, which has appeared in the literature over the past several years and occurs in both children and adults. As suggested by Dr. Kelly, it is hoped that the recent article by Cremer, et al., and our case report will lead to further study of propofol and the possible cause(s) of this rare but serious potential complication of long-term propofol infusions.

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