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Should We Use Psychostimulant Drugs to Boost the Emergence from General Anesthesia?

To the Editor:

Recently, Chemali *et al.*[1] showed that psychostimulants can accelerate the emergence from propofol anesthesia as evidenced by a faster recovery of the righting reflex and by signs of electroencephalogram activation after the injection of methylphenidate during propofol infusion. The authors believe that methylphenidate can be safely used in a clinical setting to facilitate the awakening from prolonged propofol anesthesia or in patients overly sedated by propofol. In our view, the use of psychostimulants such as methylphenidate as emergence drugs may lead to undesirable consequences, especially in the abovementioned subsets of patients.

It has been recently suggested that sequential activation of consciousness, connectedness to the environment, and responsiveness may be prerequisites for the smooth and uneventful emergence from anesthesia.[2] Switching on the connectedness or responsiveness before the consciousness is fully recovered from the effect of GABAergic drugs may be a cause of cognitive dysfunction or even delirium on emergence.[2,3] Although connectedness to external stimuli is likely to rely on norepinephrinergic signaling,[4] responsiveness probably requires the engagement of the basal ganglia and is subject to dopaminergic modulation in the striatum.[5] Methylphenidate can increase extracellular levels of both norepinephrine and dopamine in cortical and subcortical areas.[6–9] We believe that administering methylphenidate during propofol infusion or immediately after its termination and before the anesthetic is eliminated and consciousness sufficiently restored would interrupt the natural sequential switching-on of consciousness–connectedness–responsiveness and may result in postoperative cognitive dysfunction.

We also suspect that accelerated emergence in otherwise uncomplicated anesthesia cases may be unpleasant, similar to sudden and forced awakening from sleep.[10] The authors themselves noticed that the electroencephalogram pattern after methylphenidate injection during propofol infusion was not exactly a return to a normal awake state: rather, the electroencephalogram showed signs of overactivation.[1] Administration of methylphenidate at doses comparable to those used in this study causes an increase in locomotion in rats.[11,12] If the authors had examined the behavior of rats awakened from anesthesia by methylphenidate and compared it with that of animals allowed to naturally awaken from propofol, they would probably have found increased locomotor activity in the former group. The human equivalent of rat hyperlocomotion may be restlessness and agitation, both of which are undesirable and can complicate the postoperative period.

Finally, many stimulant drugs with a dopaminergic mechanism of action, including methylphenidate, lead to the so-called rebound hypersomnolence, evidenced by a period of enhanced compensatory sleep after drug-induced waking.[13,14] For methylphenidate, rebound hypersomnolence occurs at about 3 h after its intraperitoneal administration in rats.[14] It is unclear whether this phenomenon could be potentiated by residual sedation after propofol anesthesia. However, such potentiation is likely to occur and may have detrimental effects in overly sedated patients and, therefore, should be examined before the drug is used in humans.

In conclusion, the results of the study by Chemali *et al.* certainly enrich our knowledge about the mechanisms of anesthesia and prepare us for possible drug interactions in patients on methylphenidate scheduled for surgery. However, before proceeding to examine the ability of methylphenidate to accelerate the emergence from propofol anesthesia in patients, especially in those with increased drug-induced GABAergic tone, it seems prudent to investigate the effects of methylphenidate on postanesthetic cognitive function in animals. Meanwhile, we can still rely on the natural emergence from anesthesia caused by physiologic elimination of the anesthetic drug. Fortunately, with the ever-improving pharmacokinetic profiles of modern anesthetic drugs, we do not have to wait too long.

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In Reply:

The concern raised by Petrenko *et al.* regarding the possibility of delirium and cognitive dysfunction with methylphenidate administration is based on a hypothesis and not on data reported from humans receiving the drug. A review of the literature suggests that delirium and cognitive dysfunction are uncommon when methylphenidate is administered to patients under general anesthesia.

In 1958, Christensen[1] reported his experience administering intravenous methylphenidate to enhance recovery from barbiturate general anesthesia for dental procedures. The only side effect reported was insomnia in a "few" patients who received relatively high doses of methylphenidate (40–50 mg) late in the day. There was no mention of delirium or cognitive dysfunction. In fact, the author wrote that "patients move out of the office rapidly and of their own power. Moreover, because of Ritalin, they are more alert on leaving the office, and we have little fear of their not getting home safely."

In the same year, Gale[2] reported the effects of intravenous methylphenidate on recovery from thiopental and nitrous oxide general anesthesia. On average, across all dose ranges of methylphenidate, the patients who received methylphenidate had significantly faster recovery compared with controls. The incidence of postoperative crying and "excitement" was unchanged between the control group and methylphenidate group.

In 1961, Roberts[3] reported the results of a double-blind study on the effects of intramuscular methylphenidate administered on the way to the recovery room after surgery. Six of 174 patients in the methylphenidate group and three of 120 patients in the placebo group had either restlessness, crying, or thrashing around.

In 1980, Dodson and Fryer[4] conducted a study to test the effects of methylphenidate on patients under halothane or fentanyl anesthesia. The authors reported that four of 31 patients who received methylphenidate were crying and restless, whereas none of the 32 control patients who received placebo exhibited this side effect. One patient who received methylphenidate had an unexplained episode of catatonia that resolved spontaneously after 40 min. This is the only study that suggested a higher incidence of undesirable behavioral side effects with methylphenidate administration.

All the aforementioned studies have shortcomings such as small sample size, no standardized anesthetic regimen, lack of patient randomization, and/or lack of clearly defined behavioral endpoints. There is no human data for methylphenidate administration during propofol general anesthesia, but in our opinion the available evidence (particularly Gale's study with thiopental,[2] which is arguably the most similar anesthetic to propofol) suggests that methylphenidate is unlikely to cause delirium or cognitive dysfunction.

In our study using adult rats, we found that administration of methylphenidate during continuous propofol general anesthesia induced an electroencephalogram pattern that was consistent with arousal, yet distinct from the baseline awake state.[5] However, we did not conclude that the electroencephalogram "showed signs of overactivation" as Petrenko *et al.* state. Although methylphenidate administration during continuous propofol general anesthesia decreased delta power (fig. 5C),[5] the peak power after methylphenidate was at a lower frequency than the baseline awake state (fig. 5D), suggesting that neurophysiological features of both the anesthetized and awake states were present. This makes intuitive sense, because an anesthetizing dose of propofol was still present when methylphenidate was administered.

In humans, the $T_{1/2}$ for clearance of methylphenidate from the brain is 90–120 min,[6] suggesting that the activity of methylphenidate is likely to persist long after the effects of propofol have dissipated. Therefore, although rebound hypersomnolence after methylphenidate may occur several hours after administration, potentiation of this phenomenon by residual propofol is highly unlikely.