Active Emergence from Propofol General Anesthesia Is Induced by Methylphenidate

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ABSTRACT

Background: A recent study showed that methylphenidate induces emergence from isoflurane general anesthesia. Isoflurane and propofol are general anesthetics that may have distinct molecular mechanisms of action. The objective of this study was to test the hypothesis that methylphenidate actively induces emergence from propofol general anesthesia.

Methods: Using adult rats, the effect of methylphenidate on time to emergence after a single bolus of propofol was determined. The ability of methylphenidate to restore righting during a continuous target-controlled infusion (TCI) of propofol was also tested. In a separate group of rats, a TCI of propofol was established and spectral analysis was performed on electroencephalogram recordings taken before and after methylphenidate administration.

Results: Methylphenidate decreased median time to emergence after a single dose of propofol from 735 s (95% CI: 598–897 s, n = 6) to 448 s (95% CI: 371–495 s, n = 6). The difference was statistically significant (P = 0.0051). During continuous propofol anesthesia with a median final target plasma concentration of 4.0 μg/ml (95% CI: 3.2–4.6, n = 6), none of the rats exhibited purposeful movements after injection of normal saline. After methylphenidate, however, all six rats promptly exhibited arousal and had restoration of righting with a median time of 82 s (95% CI: 30–166 s). Spectral analysis of electroencephalogram data demonstrated a shift in peak power from δ (less than 4 Hz) to θ (4–8 Hz) and β (12–30 Hz) after administration of methylphenidate, indicating arousal in 4/4 rats.

Conclusions: Methylphenidate decreases time to emergence after a single dose of propofol, and induces emergence during continuous propofol anesthesia in rats. Further study is warranted to test the hypothesis that methylphenidate induces emergence from propofol general anesthesia in humans.

What We Already Know about This Topic

• The psychostimulant methylphenidate was recently found to induce emergence from isoflurane anesthesia in rats, but its effects on anesthesia produced by other agents is unclear.

What This Article Tells Us That Is New

• Methylphenidate enhanced emergence from intravenous propofol in rats, which was accompanied by a shift in the electroencephalogram to higher frequencies.

• Further studies are required to determine whether methylphenidate might provide a useful agent to facilitate emergence from general anesthesia in humans.

Anesthesiologists routinely reverse the actions of many drugs including opioids, benzodiazepines, muscle relaxants, and anticoagulants. However, emergence from general anesthesia is still treated as a passive process, dictated by the pharmacokinetics of anesthetic drug clearance. The classic approach of developing drugs that antagonize the actions of general anesthetics at the molecular level has not been feasible, because of the lack of clearly defined molecular targets through which general anesthetics induce loss of consciousness.

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Received for publication November 6, 2011. Accepted for publication February 10, 2012. Supported by grant nos. DP1-OD003646 and K08-GM094394 from the National Institutes of Health, Bethesda, Maryland, and the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital. Presented in part at annual meetings of the Society for Anesthesia and Sleep Medicine, October 14, 2011, Chicago, Illinois, and the Society for Neuroscience, November 13, 2011, Washington, D.C.

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However, at the level of neural circuits and systems, there is growing evidence to suggest that arousal pathways play important roles in emergence from general anesthesia.\textsuperscript{1–10} We recently reported that methylphenidate, an inhibitor of dopamine and norepinephrine reuptake transporters, actively induces emergence from isoflurane general anesthesia in rats.\textsuperscript{11} Methylphenidate restored the righting reflex, induced electroencephalogram changes consistent with arousal, and increased respiratory drive. The behavioral and respiratory effects induced by methylphenidate were inhibited by droperidol, supporting the idea that methylphenidate induces arousal by activating a dopaminergic arousal pathway.

Propofol is a widely used intravenous general anesthetic thought to produce its effects by enhancing the function of specific \(\gamma\)-aminobutyric acid type A receptors that contain \(\beta_3\) subunits. Transgenic mice harboring a point mutation in the \(\beta_3\) subunit of the \(\gamma\)-aminobutyric acid type A receptor are resistant to the anesthetizing effects of propofol and etomidate but not volatile anesthetics,\textsuperscript{12,13} suggesting that the molecular mechanisms of action may be distinct for these two classes of general anesthetics. However, because methylphenidate likely induces emergence from isoflurane general anesthesia by activating monoaminergic arousal pathways rather than molecular level antagonism, we hypothesized that methylphenidate induces emergence from propofol anesthesia.

To test this hypothesis a rodent model was used to determine the effect of methylphenidate \textit{versus} normal saline (vehicle) on time to emergence after a bolus dose of propofol. We also investigated whether methylphenidate restores the righting reflex during a continuous TCI of propofol. Finally, we performed spectral analysis on electroencephalogram recordings taken during continuous TCIs of propofol to test whether methylphenidate induces neurophysiological evidence of arousal.

Materials and Methods

\textbf{Animal Care and Use}

Animal studies were approved by the Subcommittee on Research Animal Care, Massachusetts General Hospital, Boston, Massachusetts, which serves as our Institutional Animal Care and Use Committee. Ten male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 375–508 g were used for these studies. Six rats were used for the propofol bolus experiments and the continuous infusion experiments, in random order. At least 3 days of rest were provided between experiments. Four additional rats with implanted extradural electrodes were used for the electroencephalogram experiments. Animals were kept on a standard day-night cycle (lights on at 7:00 AM, and off at 7:00 PM), and all experiments were performed during the day.

\textbf{Preparation and Delivery of Drugs}

Isoflurane, methylphenidate hydrochloride, and propofol were obtained from Henry Schein (Melville, NY), Sigma-Aldrich (St. Louis, MO), and APP pharmaceuticals (Shauburg, IL) respectively. Sterile normal saline, methylphenidate, and propofol were always administered intravenously. Methylphenidate was weighed, dissolved in 0.5 ml of normal saline, and sterile filtered immediately before administration. The IV tubing (approximate volume 0.6 ml) was always flushed with 2 ml of normal saline after a bolus dose of propofol or methylphenidate was administered, to ensure complete delivery of drug. Investigators were not blinded (\textit{i.e.}, the identity of the administered drug was always known).

For continuous propofol infusions, STANPUMP was run on an IBM Thinkpad T43 computer interfaced with a Physio 22 syringe pump (Harvard Apparatus, Holliston, MA). The pharmacokinetic file for propofol in rats was based on data published by Knibbe et al.\textsuperscript{14} and kindly provided by Dr. Steven L. Shafer, Columbia University, New York, NY. A constant plasma target concentration mode was selected and the drug was delivered through a dedicated lateral tail vein IV catheter.

\textbf{Time to Emergence After Propofol Bolus}

A single 24-gauge IV catheter was placed in a lateral tail vein during brief general anesthesia with isoflurane (2% to 3%) in oxygen, and then the animal was allowed to fully recover from the isoflurane general anesthetic in room air. At least 10 min after returning to a baseline level of activity, a bolus dose of propofol (8 mg/kg IV) was administered. This dose was chosen because it is approximately twice the published EC\textsubscript{50} dose for loss of righting.\textsuperscript{15} All rats lost the righting reflex within 30 s, and were gently placed in the supine position on a heating pad. Forty-five seconds after administration of propofol, methylphenidate (5 mg/kg IV) or normal saline (vehicle) was administered. Time to emergence was defined as the time from administration of propofol until restoration of the righting reflex (\textit{i.e.}, all four paws touching the floor). The same six rats were used on different days (at least 3 days apart) for both the normal saline group and the methylphenidate group. A crossover design was used (\textit{i.e.}, half of the animals received normal saline on the first day and methylphenidate on the second day, and the other half underwent the experiments in reverse order).

\textbf{Administration of Methylphenidate during Continuous Propofol General Anesthesia}

Rats were anesthetized in an induction chamber with 2% to 3% isoflurane in oxygen before the placement of two 24-gauge IV catheters, one on each lateral tail vein. One catheter was used as a dedicated line for the continuous TCI of propofol, and the other was used for bolus administration of methylphenidate or normal saline. The catheter used for bolus administration was kept open by using a second syringe pump that continuously infused normal saline at a rate of 2 ml/h. After initiating the propofol infusion, isoflurane was
Discontinued and the rats were placed in the supine position on a heating pad in room air. A rectal temperature probe was used to maintain core body temperature at 36.5°–37.4°C.

To establish the minimum target plasma concentration of propofol sufficient to maintain loss of righting, the propofol infusion was initiated with a target plasma dose of 5.0 μg/ml. If the rat did not exhibit any purposeful movements, the propofol concentration was lowered by 0.5 μg/ml every 10 min. If the rat exhibited purposeful movements, the propofol concentration was increased until purposeful movements were no longer observed, and then lowered by 0.5 μg/ml every 10 min. The final target concentration was defined as 0.5 μg/ml above the highest dose at which purposeful movements were observed, and fixed for the remainder of the experiment. Pilot studies indicated that this protocol most reliably provided a steady state propofol general anesthetic with continuous loss of righting.

Establishing the final dose of propofol took a minimum of 45 min, during which time the rats inhaled room air and were not exposed to isoflurane. Fifteen minutes after arriving at the final target concentration for propofol, a bolus of normal saline was administered and the temperature probe was removed, to confirm that these mildly stimulating maneuvers were insufficient to induce an arousal response. At the final dose of propofol, no animal exhibited purposeful movement after bolus injection of normal saline or removal of the temperature probe. Five minutes after the normal saline bolus, methylphenidate (5 mg/kg IV) was administered. The experiment was terminated when the rat regained the righting reflex or when 30 min had elapsed after methylphenidate administration, whichever came first.

**Electroencephalogram Electrode Placement, Recording, and Spectral Analysis**

Extradural electroencephalogram electrodes were surgically implanted at least 7 days before recording. General anesthesia was induced and maintained with isoflurane. A microdrill (Patterson Dental Supply Inc., Wilmington, MA) was used to make four holes at the following stereotactic coordinates: A0L0, A6L3, A6L-3, and A10L2 relative to the λ.16 An electrode with mounting screw and socket (Plastics One, Roanoke, VA) was screwed into each hole, and the sockets were inserted in a pedestal (Plastics One). The screws, sockets, and pedestal were all permanently fixed with dental acrylic cement, and the animal underwent a minimum recovery period of 7 days.

On the day of recording, the potential difference between electrodes A0L0 and A6L3 (right somatosensory cortex) or between electrodes A0L0 and A6L-3 (left somatosensory cortex) was recorded based on which signal gave less motion artifact. The signal was referenced to A10L2 and recorded using a QP511 Quad AC Amplifier System (Grass Instruments, West Warwick, RI) and a USB- 6009 14-bit data acquisition board (National Instruments, Austin, TX). The sampling rate was 512 Hz, and no line filter was used. Data were filtered between 0.3 Hz and 50 Hz. A 10-min baseline electroencephalogram was recorded during the awake state before the induction of general anesthesia.

In order to decrease motion artifacts associated with righting attempts, a higher dose of propofol was used for these studies. Using the same procedure described in Administration of Methylphenidate During Continuous Propofol General Anesthesia, the final target concentration of propofol was established and maintained at 1.0 μg/ml above the highest dose at which purposeful movements were observed. After 15 min at the final dose of propofol, the electroencephalogram signal was recorded for an additional 10 min, and then normal saline was injected. None of the animals exhibited purposeful movement during or after administration of normal saline. Five minutes later, methylphenidate (5 mg/kg IV) was administered. Although we initially attempted to perform the electroencephalogram experiments at the same dose of propofol as the experiments described in the previous section, the animals moved too vigorously after the administration of methylphenidate. Therefore the higher dose of propofol was necessary to attenuate the methylphenidate-
induced arousal response and reduce motion artifacts on the electroencephalogram.

Spectral analysis was performed using Matlab R2010b (Mathworks, Natick, MA) and Chronux software (Cold Spring Harbor, NY), as previously described. Briefly, mean power spectra were compared before and after methylphenidate administration using Kolmogorov-Smirnov tests. To determine the difference between two spectra, a two-sample Kolmogorov-Smirnov test was performed on the spectral power as a function of frequency computed from the 30 windows in the premethylphenidate and postmethylphenidate periods. We used a Bonferroni correction to adjust the significance level for multiple hypothesis-testing.

**Statistical Analysis**

Prism 4.03 (Graphpad Software, San Diego, CA) and Matlab R2010b (Mathworks, Natick, MA) were used for statistical analysis. Statistical significance was defined as a P value < 0.05. The Mann–Whitney test was used to test the hypothesis that methylphenidate decreases time to emergence after a bolus dose of propofol.

To compare the effect of methylphenidate versus normal saline on return of righting during continuous propofol general anesthesia, we used a Bayesian Monte Carlo procedure to compute Bayesian 95% (confidence intervals) CIs for the difference in the righting probabilities of the two groups. We also used the algorithm to compute the probability that the righting probability in one group is greater than the righting probability in the other group. Let denote the probability of righting for the animals in group , where is the methylphenidate group and is the saline group. If there are animals in each group, let be the number of animals in group that right. Because each animal in a given group either has return of the righting reflex or does not, the outcome of the experiment for each animal is Bernoulli, and the joint distribution or likelihood for the animals in group is the binomial model.

\[
f(k_i | p_i) = \binom{n}{k_i} p_i^{k_i} (1-p_i)^{n-k_i}. \tag{1}
\]

To perform a Bayesian analysis we assume that the prior density for is the beta probability model \(f(p_i) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} p_i^{\alpha-1}(1-p_i)^{\beta-1}, \tag{2}\)

for \(p_i \in (0,1)\), parameters \(\alpha > 0\) and \(\beta > 0\) and \(\Gamma(\alpha) = \int_0^\infty x^{\alpha-1} \exp(-x)dx\) is the standard gamma function. It follows that the posterior density for group is the gamma density \(\text{f}(p_i | k_i) = \frac{\Gamma(n + \alpha + \beta)}{\Gamma(k_i + \alpha)\Gamma(n - k_i + \beta)} \times p_i^{k_i+a-1}(1-p_i)^{n-k_i+b-1}. \tag{3}\)

For our analyses we take \(\alpha = \beta = 1\) in Eq. 2 so that the prior density for both groups is the uninformative, uniform probability density on the interval \((0, 1)\). Given the posterior densities for the methylphenidate and the saline groups, we compute the posterior density \(f(p_m | p_i, k_i)\) by using the following Monte Carlo algorithm:

1. Draw \(p_m\) from \(f(p_m | k_m)\)
2. Draw \(p_i\) from \(f(p_i | k_i)\)
3. Compute \(p_m - p_i\)
4. Do 1–3 10,000 times.

The histogram of the 10,000 \(p_m - p_i\) values is a Monte Carlo approximation to the posterior density \(f(p_m | p_i, k_i)\). The lower and upper limits of the 95% Bayesian CI are 250th smallest value and 9,750th smallest value in the Monte Carlo sample, respectively. We compute the posterior probability that \(p_m > p_i\) as \(\Pr(p_m > p_i | k_m, k_i) = t/10,000\) where \(t\) is the number of times that \(p_m > p_i\) in the Monte Carlo sample. Unlike CIs computed using frequentist methods, the Bayesian 95% CIs can be interpreted as having probability = 0.95 that the value of \(p_m - p_i\) lies

![Fig. 2. Methylphenidate induces emergence during a continuous target-controlled infusion of propofol.](image)

(A) The final target plasma concentration of propofol was established at 0.5 \(\mu\)g/ml above the highest dose at which purposeful movements were observed, and maintained for 15 min before normal saline (vehicle) was injected. Five minutes later, methylphenidate (5 mg/kg IV) was administered. The propofol infusion was continued at the same dose. (B) None of the rats exhibited an arousal response during the 5 min after normal saline administration (n = 6). However, methylphenidate induced a profound arousal response and restored the righting reflex within 4 min in all rats (n = 6), despite continuous propofol general anesthesia. **Posterior probability > 0.95.**
between the lower and upper limits of the interval based on the data in the current sample. We used this Monte Carlo algorithm in our previous studies using methylphenidate to induce active emergence from isoflurane general anesthesia.

Results

Methylphenidate Decreases Time to Emergence after a Propofol Bolus

Figure 1A summarizes the protocol for this experiment. As shown in figure 1B, the median time to emergence for animals that received normal saline was 735 s (95% CI: 598–897 s, n = 6) versus 448 s (95% CI: 371–495 s, n = 6) for animals that received methylphenidate. The median difference in time to emergence between these two groups was 282 s (95% CI: 166–458 s, Mann–Whitney U test). This median difference was statistically significant (P = 0.0051).

Methylphenidate Restores the Righting Reflex during Continuous Propofol General Anesthesia

Figure 2A summarizes the protocol for this experiment. The final target concentration of propofol was maintained at a dose 0.5 μg/ml above the highest dose at which purposeful movements were observed, and fixed for the remainder of the experiment. The median final target plasma concentration of propofol was 4.0 (95% CI: 3.2–4.6, n = 6). The results of the experiment are shown in figure 2B. During continuous propofol anesthesia, none of the rats exhibited purposeful movements after IV injection of normal saline or removal of the temperature probe (n = 6). However, after administration of methylphenidate (5 mg/kg IV), all of the rats promptly exhibited signs of arousal (e.g., lifting of the head, blinking of the eyes, twisting of the torso, kicking, clawing, and grooming) and had restoration of righting within 4 min, with a median time of 82 s (95% CI: 30–166 s, n = 6). The Bayesian 95% CI for the difference in the probabilities to have return of righting between rats in the methylphenidate group and those in the normal saline group was 0.373 to 0.968. The posterior probability that pm > ps was 0.9995.

Methylphenidate Induces Changes in Electroencephalogram Spectral Content that Correlate with Increased Arousal

The electroencephalogram was recorded from four rats with preimplanted extradural electrodes over the somatosensory cortex. In order to minimize motion artifacts, the final target concentration of propofol was maintained at a higher dose (1.0 μg/ml above the highest dose at which purposeful movements were observed), and fixed for the remainder of the experiment. Typical raw electroencephalogram traces recorded from a single rat are shown in figure 3. In the awake state before the administration of any drugs, animals showed an active high-frequency, low-amplitude electroencephalogram pattern, which changed to a low-frequency, high-amplitude pattern during the TCI of propofol.

Although the electroencephalogram pattern did not change after injection of normal saline or removal of the temperature probe, administration of methylphenidate (5 mg/kg IV) induced a shift back to an active high-frequency, low-amplitude pattern similar to that observed during the awake state. This change persisted for more than 10 min despite the continuous TCI of propofol. After the administration of methylphenidate, none of the rats had restoration of righting at this higher dose of propofol, but all four exhibited varying behavioral signs of arousal (e.g., opening of the eyes, lifting of the head, kicking, and others). To assess changes in electroencephalogram power over time, spectrograms were computed from the continuous unfiltered electroencephalogram data recorded from each animal. Typical results from an individual rat are shown in figure 4. During the awake state, electroencephalogram power was mainly in the θ frequency range (4–8 Hz). How-
ever, the TCI of propofol caused a large increase in $\delta$ power (less than 4 Hz). Although IV injection of normal saline produced no appreciable change in the power spectrum, administration of methylphenidate (5 mg/kg IV) produced a prompt reduction in $\delta$ power, and increased $\theta$ (4–8 Hz) and $\beta$ power (12–30 Hz), providing evidence for a new arousal state distinct from the baseline awake state.

Figure 5 shows spectrograms and power spectra from four different animals during continuous TCIs of propofol, with the results of the Kolmogorov-Smirnov test computed from 2-min time windows before and after methylphenidate administration. At a 0.05 significance level, the two-sided Kolmogorov-Smirnov test with Bonferroni correction rejects the null hypothesis at all frequencies except those marked with white squares. Methylphenidate (5 mg/kg IV) decreased $\delta$ power and increased $\theta$ (4–8 Hz) and $\beta$ power in all four animals. The difference in power before and after methylphenidate was statistically significant at most frequencies between 0–30 Hz.

**Discussion**

In this study we found that methylphenidate induces emergence from propofol general anesthesia in rats. Methylphenidate decreased time to emergence after a propofol bolus, and induced emergence during a continuous TCI of propofol. The effects of methylphenidate (5 mg/kg IV) were dependent on the dose of propofol. When the target plasma concentration of propofol was fixed at a dose 0.5 µg/ml above the highest dose at which purposeful movements were observed, methylphenidate restored the righting reflex. At a higher dose of propofol, methylphenidate induced electroencephalogram changes and varying behaviors consistent with arousal, but did not restore the righting reflex. The electroencephalogram pattern induced by methylphenidate during propofol general anesthesia was not identical to the pattern observed during the baseline awake state in the absence of drugs, suggesting that the two arousal states are distinct.

Although isoflurane general anesthesia was used for tail vein IV placement, the procedure typically took less than 5 min, and isoflurane was promptly discontinued after the IV was secured. For the bolus experiments, propofol was delivered at least 10 min after the animal recovered a baseline level of normal activity. For the continuous infusion experiments, establishing the final dose of propofol took a minimum of 45 min, during which time the rats inhaled room air and were not exposed to isoflurane. In both cases, residual isoflurane levels were likely minimal at the time methylphenidate was administered.

There has been a growing interest in the role of ascending arousal pathways in emergence from general anesthesia. The injection of nicotine in the central medial thalamus induces emergence from sevoflurane anesthesia in rats, and physostigmine, a centrally acting cholinesterase inhibitor, restored consciousness in human volunteers during sevoflurane anesthesia as well as propofol anesthesia. These studies demonstrate that emergence from general anesthesia can be achieved by activating central cholinergic neurotransmission. It was recently reported that injection of the arousal-promoting neurotransmitters histamine or norepinephrine into the nucleus basalis magnocellularis induces behavioral and neurophysiological evidence of arousal during general anesthesia, providing evidence that monoaminergic arousal pathways are also important for emergence from general anesthesia.

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**Fig. 4.** Spectral analysis of electroencephalogram data reveals a shift in power induced by methylphenidate during a continuous target-controlled infusion of propofol. Warm colors (e.g., red) represent higher power at a given frequency, whereas cool colors (e.g., blue) represent lower power. (A) A representative spectrogram computed from a rat in the awake state shows predominance of $\theta$ power (4–8 Hz). (B) A representative spectrogram computed from a rat during propofol general anesthesia shows predominance of $\delta$ power (less than 4 Hz) before and after administration of normal saline. However, administration of methylphenidate (5 mg/kg IV) promptly reduced $\delta$ power, and increased $\theta$ (4–8 Hz) and $\beta$ power (12–30 Hz), providing evidence for a new arousal state distinct from the baseline awake state. MPH = methylphenidate.
We recently reported that methylphenidate induces emergence from isoflurane general anesthesia, an effect that is inhibited by droperidol. Methylphenidate acts by blocking dopamine and norepinephrine reuptake transporters, and it likely antagonizes the effects of isoflurane and propofol by activating a combination of dopaminergic, noradrenergic, and/or histaminergic arousal pathways. Transgenic mice harboring a point mutation in the GABA<sub>A</sub> receptor are highly resistant to the anesthetizing effects of propofol but not volatile anesthetics, suggesting that propofol and isoflurane may produce general anesthesia by distinct molecular mechanisms. Although the present study does not prove the mechanism of action of methylphenidate, the finding that methylphenidate induces emergence from both isoflurane and propofol general anesthesia further supports the hypothesis that methylphenidate acts by activating monoaminergic arousal pathways at the circuit level, rather than antagonizing general anesthetics at the molecular level.

In our previous study we used plethysmography to show that methylphenidate also increases respiratory drive in rats anesthetized with isoflurane. We concluded that the increase in minute ventilation induced by methylphenidate likely accelerated isoflurane elimination and contributed to the decrease in time to emergence. In this study we did not perform plethysmography experiments during propofol general anesthesia, because unlike inhaled anesthetics, the elimination of propofol does not involve the pulmonary system. However, there is considerable evidence that activating dopaminergic neurotransmission increases respiratory drive, so it is reasonable to predict that methylphenidate would also stimulate breathing during propofol general anesthesia. It is noteworthy that the animals in the present study inhaled room air (unlike the animals in our previous study, which inhaled pure oxygen as the carrier gas for isoflurane), demonstrating that hyperoxia is not necessary for methylphenidate to induce emergence from general anesthesia.

To our knowledge, this is the first study to report the use of a STANPUMP-based TCI to maintain propofol general anesthesia in rodents. The rat pharmacokinetic profile was based on allometric extrapolations comparing adults, children...
Children, and rats. Our results suggest that these kinetic parameters can be used to maintain a reliable steady-state general anesthetic with propofol. However, one weakness of this study is that we did not assay the propofol concentrations in blood over time to confirm that the TCI was providing a stable plasma concentration. Because we used long equilibration times and a careful titration protocol to arrive at the final dose of propofol, however, it is unlikely that large changes in the effect site concentration of propofol were occurring at the time of methylphenidate administration.

It has been reported that patients taking methylphenidate have an increased requirement for propofol, which agrees with the findings of this study. Further study is warranted to test the hypothesis that methylphenidate induces emergence from propofol general anesthesia in humans. Methylphenidate may be useful to restore consciousness in patients oversedated with propofol, and to induce emergence from propofol general anesthesia after prolonged infusions. Methylphenidate has a well-established safety profile in both children and adults for the treatment of Attention Deficit Hyperactivity Disorder. The results of the present study suggest that methylphenidate may be clinically useful to induce emergence from propofol general anesthesia. The availability of such a drug may lead to improved patient safety and operating room efficiency.

The authors thank Steven L. Shafer, M.D., Professor of Anesthesiology, Columbia University, New York, New York, for kindly providing the propofol pharmacokinetics file for rats in STANPUMP.

References