Caffeine Accelerates Emergence from Isoflurane Anesthesia in Humans

A Randomized, Double-blind, Crossover Study

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ABSTRACT

Background: There are currently no drugs clinically available to reverse general anesthesia. We previously reported that caffeine is able to accelerate emergence from anesthesia in rodents. This study was carried out to test the hypothesis that caffeine accelerates emergence from anesthesia in humans.

Methods: We conducted a single-center, randomized, double-blind crossover study with eight healthy males. Each subject was anesthetized twice with 1.2% isoflurane for 1 h. During the final 10 min of each session, participants received an IV infusion of either caffeine citrate (15 mg/kg, equivalent to 7.5 mg/kg of caffeine base) or saline placebo. The primary outcome was the average difference in time to emergence after isoflurane discontinuation between caffeine and saline sessions. Secondary outcomes included the end-tidal isoflurane concentration at emergence, vital signs, and Bispectral Index values measured throughout anesthesia and emergence. Additional endpoints related to data gathered from postanesthesia psychomotor testing.

Results: All randomized participants were included in the analysis. The mean time to emergence with saline was 16.5 ± 3.9 (SD) min compared to 9.6 ± 5.1 (SD) min with caffeine ($P = 0.002$), a difference of 6.9 min (99% CI, 1.8 to 12), a 42% reduction. Participants emerged at a higher expired isoflurane concentration, manifested more rapid return to baseline Bispectral Index values, and were able to participate in psychomotor testing sooner when receiving caffeine. There were no statistically significant differences in vital signs with caffeine administration and caffeine-related adverse events.

Conclusions: Intravenous caffeine is able to accelerate emergence from isoflurane anesthesia in healthy males without any apparent adverse effects. **(Anesthesiology 2018; 129:912-20)**

ALTHOUGH pharmacologic reversal agents exist for many categories of drugs routinely used by anesthetists including opioids, benzodiazepines, and paralytics, there are currently no drugs available to reverse the coma-like state induced by general anesthetics.[1] Identification of such drugs would be of considerable utility in clinical practice. Patients recover from anesthesia with varying time courses, dependent upon a number of factors that are beyond the clinician's control, including but not limited to genetics, comorbidities, and age.[2] After emergence, cognitive and psychomotor compromise can persist for minutes to hours as evidenced by delayed reaction time, memory impairment, and problems with motor coordination. Prolonged recovery delays return to baseline, safe functioning, and independence and engenders significant costs in the form of extended stays in postanesthesia recovery units. Seniors represent a particularly vulnerable population in this regard because recovery time after anesthesia can be markedly prolonged from hours to days in some cases.[3]

There have been ongoing efforts to reverse the effects of anesthesia in animals, most of which involved intracerebral injection of various agents including a cyclic adenosine monophosphate (cAMP) analog,[4] an antibody directed against potassium channels,[5] a cholinesterase inhibitor and muscarinic agonist,[6] and nicotine.[7] Although compelling, these studies are of limited clinical utility because they involve injecting drugs directly into the brain. More recently, aminophylline has shown promise in accelerating emergence from anesthesia.[8–10] Finally, Solt *et al.*[2,11] have shown that methylphenidate

Editor's Perspective

What We Already Know about This Topic

- Caffeine may speed anesthetic emergence

What This Article Tells Us That Is New

- The authors tested the hypothesis that caffeine speeds anesthetic emergence
- Volunteers anesthetized with isoflurane were given caffeine (equivalent to 7.5 mg base) or placebo in a blinded crossover trial
- When given caffeine, the volunteers emerged more quickly and at a higher isoflurane concentration

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version. Presented in abstract form at the Association of University Anesthesiologists annual meeting in Chicago, Illinois, April 27, 2018.

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accelerated emergence from anesthesia in rats, implicating D_1 dopamine receptor activation as the mechanistic basis of their observed effect.[12,13] Of note, activation of D_1 receptors is known to produce downstream elevation of $[cAMP]_i$.[14,15]

Previously, we demonstrated that a series of drugs that elevate $[cAMP]_i$ could dramatically accelerate emergence from anesthesia when administered intravenously in rats.[16] Of the three drugs tested, caffeine was most effective. Here we hypothesize that caffeine is able to accelerate emergence from anesthesia in humans and may represent a useful adjunct to modern anesthesiology.

Materials and Methods

Study Design

A single-center double-blind two-way crossover trial design was employed (fig. 1). Each subject attended the first session for preanesthesia evaluation, consent explanation, and psychometric test training. If a subject met the criteria and signed the consent, the subject was included in the randomization. Participants underwent two sessions of general anesthesia administered a minimum of 2 weeks apart. In randomized fashion, each subject received, during the final 10 min of anesthesia, a saline infusion during one of the sessions and a 15 mg/kg caffeine citrate infusion (corresponding to 7.5 mg/kg of caffeine base) during the other. Subjects and participating physicians were blinded to the identity of the infusions administered. The protocol and informed consent documents were approved by the institutional review board at the University of Chicago (Chicago, Illinois) and the Food and Drug Administration (Investigational New Drug). This study was registered at ClinicalTrials.gov (identifier NCT02567968; primary investigator, Dr. Fox) on October 5, 2015.

Participant Selection

Participants were healthy male volunteers between the ages of 25 and 40 yr who submitted to preanesthetic evaluation, electrocardiogram, and urine toxicology screens. Patients were excluded if they were overweight (body mass index greater than 30); had an activity tolerance of less than 5 metabolic equivalents; had a snoring, tiredness, observed apnea, high blood pressure-body mass index, age, neck circumference, and sex score of more than 3, indicating an elevated risk of sleep apnea; had a history of alcohol or drug abuse, seizure, or head trauma; had systemic comorbidities, mental illness, or a family history of adverse events related to anesthesia; or manifested abnormal electrocardiogram findings or positive urine toxicology.

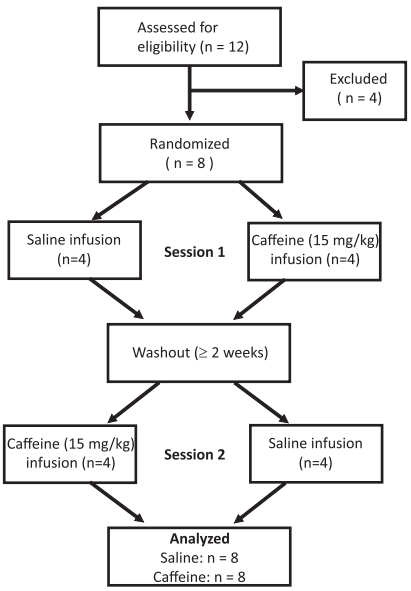

Fig. 1. Flow diagram depicting study design.

As described above, this trial employed males exclusively. The Food and Drug Administration and the University of Chicago institutional review board approved this limitation. Both the Food and Drug Administration and the institutional review board desired to limit the cohort to the smallest possible size to minimize risk. Using both males and females might increase variance. Furthermore, pregnancy tests are not 100% accurate. Anesthetics are harmful to fetuses. Thus, both groups agreed to let us complete a trial with healthy young male volunteers. If a clear effect was observed, then a different trial in healthy young females would start at a future date. This "female only" trial is now planned for the end of 2018.

Intervention

All studies were carried out in the perioperative care unit at the University of Chicago. Standard fasting guidelines were followed, and a negative toxicology screen was confirmed before each anesthetizing session. An IV catheter was inserted at the start of each session, and standard monitoring was maintained throughout; including electrocardiogram, blood pressure, respiratory rate, end-tidal CO_2 and isoflurane levels, pulse oximetry, and temperature. Additionally, Bispectral Index (BIS) monitoring was performed. This index outputs a dimensionless two-digit number between 0 and 100 that is proportional to the brain concentration of anesthetic, which in turn is correlated with an individual's level of consciousness.[17] Subjects were preoxygenated with 100% O_2 *via* a face mask and then given an IV bolus of 2 to 2.5 mg/kg propofol to induce anesthesia. A ProSeal laryngeal mask airway (Laryngeal Mask Company Limited, USA) was then inserted orally into the larynx to complete the induction phase. During the maintenance phase, participants were allowed to spontaneously breathe isoflurane (1.2%, measured as end-tidal concentration) for 60 min. At 40 min, subjects were given nausea prophylaxis with 4 mg of IV ondansetron. At 10 min before terminating the isoflurane, volunteers received an infusion during 10 min of either saline (control) or caffeine citrate.

Laryngeal mask airway devices cannot be inserted into alert/awake people, because they cause gagging. Thus, in this trial, every test subject received an injection of propofol, the induction phase, before inserting the laryngeal mask airway device. Propofol suppresses the gag response. This was

followed by administration of isoflurane for 60 min, which also suppresses gagging. After terminating the isoflurane, every test subject gagged, after their internal isoflurane levels were sufficiently diminished. This response was extremely robust.

After discontinuation of isoflurane, the subjects were allowed to emerge naturally and unperturbed. Although there was a small amount of noise from the monitoring equipment, the room was otherwise kept quiet until the subjects opened their eyes. At this time, after the subjects spontaneously opened their eyes, they were able to follow a command to open their mouths for the removal of laryngeal mask airways. We recorded the time to return of the gag reflex (which had been suppressed by anesthesia) triggered by the presence of the laryngeal mask airway, eye opening, and response to verbal commands. At 15-min intervals for 2 h after the discontinuation of the isoflurane, the subjects were asked to complete a visual analog scale and perform two validated psychomotor tests if they were awake enough to do so. The visual analog scale and the two psychomotor tests were done on a laptop computer using PsychometRx software (INC Research Toronto, Inc., Canada).

For the visual analog scale,[18] subjects were asked a series of questions to rate how they currently felt. Test subjects were shown a scale bar with a sliding cursor on a computer screen. The sliding cursor could be moved, in a continuous fashion, from a value of 0 to a value of 100, using the computer's mouse (0 = not at all, 100 = extremely). In the Sternberg test of memory,[19] participants were asked to memorize a string of two, four, and then six numbers. After each string, a computer would flash a series of random numbers on the screen, and the participant was asked whether the number shown was part of the string or not. In the divided attention task, participants were asked to fly an airplane over the center of a winding road with a joystick and simultaneously press a button whenever targets randomly flashed on the screen. The computer program tracked the root-mean-squared deviation of the plane from the center of the road. During testing, subjects completed the visual analog scale first and then the Sternberg test of memory, followed by the divided attention task. The psychomotor tests were practiced by volunteers during an orientation session and before receiving anesthesia during each session to provide a baseline, to acclimate them to the tests, and also to prevent practice effects on psychomotor testing during the experimental session. Participants were monitored in the recovery phase after anesthesia and by phone interviews for 1 week after each session to capture any study-related adverse events.

Randomization and Blinding

A research pharmacist performed the randomization using a randomization plan generator. The pharmacist masked the identity of the infusions by placing them in identically marked syringes. The appropriate syringes were delivered to one of the investigators on the day of the session. The randomized allocation schedule could only be accessed by the research pharmacist, who was not involved in the administration of the infusions.

Outcome Measures

The primary endpoint in our study was time to emergence, defined as return of the gag reflex after discontinuation of anesthesia. While we measured time to return of gag reflex, eye opening, and responsiveness to commands, we used the gag reflex as the point of awakening because it was well defined and unequivocal. Using the time for return of the gag reflex as a proxy for recovery was decided before the beginning of the trial, after completion of a pilot project with two test subjects (data not shown because the subjects were tested with a different caffeine dosage). Time to eye opening after termination of anesthesia is reported as well. Several secondary endpoints were measured, including the expired concentration of isoflurane present at emergence, as well as BIS levels, minute ventilation, mean arterial pressure, and heart rate throughout anesthesia and emergence. Additional secondary endpoints related to data gathered from postanesthesia psychomotor testing were also collated.

Statistics and Sample Size

Because this study represents the first use of caffeine for the purpose of accelerating emergence from anesthesia in humans, the parameters used to calculate sample size were derived from data we previously obtained in male rats.[16] Before this study, we completed a pilot project with two test subjects; the findings suggested that the rat data[16] adequately predicted human responses to caffeine. Sample size, estimated effect size, and α selection were based on the rat data (details in appendix). Based upon those results, the following parameters were used: an overall two-sided significance level of 0.01, 95% power, and an expected reduction in time to emergence of approximately 50%. Using these parameters, we estimated that eight subjects represented a sufficient sample size. An α level of 0.01 was chosen in light of new concerns about reproducibility in biomedical science.[20]

In our study design, participants served as their own control, and all who were randomized were included in the analysis. Significance in the comparisons between test and placebo sessions was assessed by a paired Student's *t* test. For some of the primary and secondary endpoints, a 99% CI was computed. For the BIS shown in figure 2 and the psychomotor data shown in figure 3, a two-way repeated measures ANOVA was fit with condition (saline *vs.* caffeine) and time as repeated measures factors utilizing a Greenhouse–Geisser sphericity adjustment followed by Bonferroni adjusted *post hoc* testing as needed, using Stata software (StataCorp, USA).

Adverse Event Assessment

Safety was assessed by the number of participants with adverse events. Participants were monitored in the recovery phase after anesthesia by anesthesiologists and by phone interviews for a week (postanesthesia days 0, 1, and 7) to capture any study-related adverse events. Expected side effects of general anesthesia with a supraglottic airway were

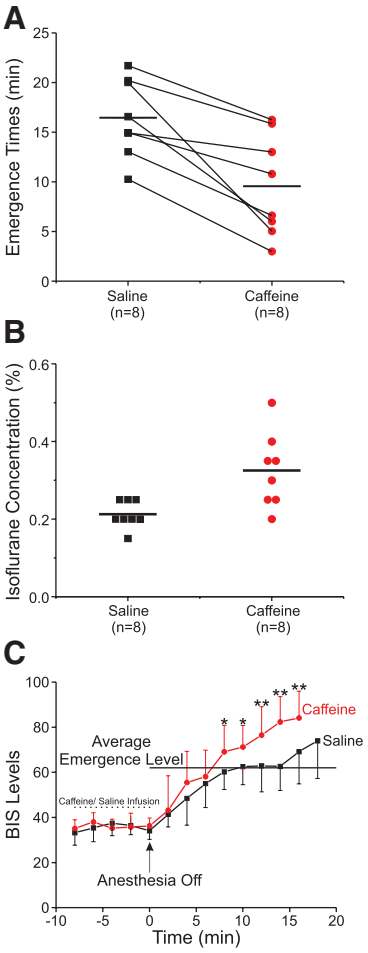

Fig. 2. Caffeine effects on emergence parameters. (*A*) Distribution of recovery times for test subjects injected with saline (*black square*) or with caffeine citrate (*red circle*). Average values for each distribution are represented by *horizontal marks*, and *line segments* connect data points from the same participant. SD for saline = 3.9 min, and SD for caffeine = 5.1 min. (*B*) Plots the distribution of end-tidal isoflurane values at emergence for test subjects infused with saline (*black square*) or with caffeine citrate (*red circle*). SD saline = 0.01, and SD caffeine = 0.03. (*C*) Bispectral Index (BIS) measurements. BIS levels are plotted at 2-min intervals encompassing infusion of caffeine or saline, emergence, and recovery. Data points are shown that are significantly different (*$P < 0.05$) and that correspond to $P < 0.001$ (**). A repeated-measures ANOVA model was fit with condition (saline *vs*. caffeine) and time as repeated factors. There was evidence for a time by condition interaction (Greenhouse–Geisser adjusted $P = 0.004$). Subsequent saline *versus* caffeine comparisons (Bonferroni adjusted) gave the following: no significant difference for times (t) of 6 min or less; t = 8 ($P = 0.037$), t = 10 ($P = 0.042$), t = 12 ($P < 0.001$), t = 14 ($P < 0.001$), and t = 16 ($P < 0.001$).

not considered adverse effects. For instance, a mild transient sore throat due to laryngeal mask airway insertion is not uncommon and was therefore not considered an adverse effect. By contrast large (greater than 20%) changes in blood pressure or heart rate after caffeine infusion would have been considered an adverse effect.

Caffeine Dosage Selection

A pilot project that enrolled two test subjects, with a dosage of 10 mg/kg of caffeine, suggested that rat data[16] adequately predicted human responses to caffeine. A higher caffeine dosage (15 mg/kg) was chosen for the current study using rat data overall effect and in consultation with the Food and Drug Administration and the University of Chicago institutional review board.

Recruitment of Test Subjects

Subjects were initially recruited by flyers describing the study and by word of mouth. Each test subject received an honorarium for each anesthesia session.

Results

Twelve subjects were assessed for eligibility (fig. 1). Four did not meet inclusion criteria. Eight male subjects ranging in age from 26 to 35 yr were randomized to receive saline or caffeine infusion during anesthetizing sessions. Recruitment started in January 2017, and the last participant completed the study in April 2017. Three test subjects were Caucasian, three were of African descent, and two were of Asian descent. Baseline caffeine consumption ranged from rare to one or two cups of coffee daily.

Time to emergence is reported in table 1. Although we also measured time to eye opening and responsiveness to commands, we preferred restitution of the gag reflex because it was well defined and unequivocal. For the eight test subjects, the mean time to emerge from anesthesia was 16.5 ± 3.9 (SD) min when receiving saline and 9.6 ± 5.1 (SD) min when receiving caffeine ($P = 0.002$). The mean difference was 6.9 min (99% CI, 1.8 to 12), corresponding to a 42% reduction. Figure 2A plots the distribution of waking times and demonstrates that every subject emerged more rapidly from anesthesia when given caffeine.

Test subjects were able to open their eyes ~1 min after they started to gag. The difference between subjects receiving saline *versus* caffeine was highly significant: time to eye opening after saline = 17.6 ± 4 (SD) min; time to eye opening after caffeine = 11.1 ± 3.8 (SD) min; $P = 0.002$. The mean difference was 6.5 min (99% CI, 1.6 to 11.4).

End-tidal isoflurane concentration was monitored throughout the anesthetizing sessions until laryngeal mask airway removal. Table 1 shows that end-tidal isoflurane concentration was higher at emergence from anesthesia when test subjects received caffeine as compared to saline (0.33 ± 0.03% *vs.* 0.21 ± 0.01%, $P < 0.015$). Figure 2B plots the distribution of end-tidal isoflurane concentrations at emergence from anesthesia for all eight test subjects, demonstrating that test subjects emerged from anesthesia at a higher end-tidal isoflurane concentration when given caffeine as compared to saline. The mean difference in end-tidal isoflurane was 0.12% (95% CI, 0.03 to 0.20).

Figure 2C shows that BIS measurements from the saline and caffeine sessions were indistinguishable during the

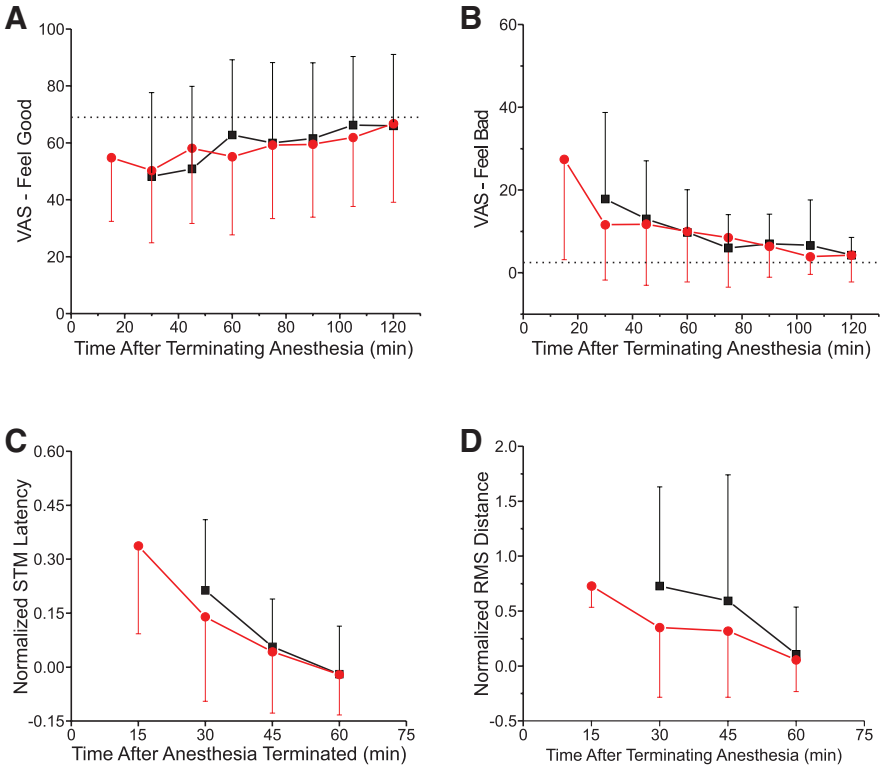

Fig. 3. Psychomotor testing. (*A*, *B*) When a visual analog scale (VAS) was used, test subjects did not report feeling better or worse after caffeine infusion. "VAS Good" and "VAS Bad" data were analyzed with a repeated-measures ANOVA. There was no evidence for a time by condition interaction (for "VAS Good," Greenhouse–Geisser adjusted $P = 0.46$; for "VAS Bad," Greenhouse–Geisser adjusted $P = 0.57$) and no overall difference between conditions (for "VAS Good," Greenhouse–Geisser adjusted $P = 0.84$; for "VAS Bad," Greenhouse–Geisser adjusted $P = 0.72$), so no further comparisons were made. (*C*) Sternberg test of memory (STM) latency. This figure plots response latency normalized to preanesthetic values. STM latency data from 30 to 60 min were analyzed with a repeated-measures ANOVA model (fit with condition [saline *vs*. caffeine] and time as repeated factors) showed no evidence for a time by condition interaction (Greenhouse–Geisser adjusted $P = 0.47$) and no overall difference between conditions (Greenhouse–Geisser adjusted $P = 0.64$), so no further comparisons were made. (*D*) Divided attention task. This graph plots the root-mean-squared deviation (RMS) from the ideal flight path normalized to preanesthetic performance. Each subject completed the psychomotor tests immediately before the anesthesia session. This corresponded to their "baseline" scores under anesthesia-free conditions. The data obtained after emergence from anesthesia were normalized to this baseline. Divided attention task RMS distance data were analyzed with a repeated-measures ANOVA model (condition [saline *vs*. caffeine] and time as repeated factors). There was no evidence for a time by condition interaction (Greenhouse–Geisser adjusted $P = 0.39$) and no overall difference between conditions (Greenhouse–Geisser adjusted $P = 0.18$), so no further comparisons were made. There was some evidence for nonnormality for the divided attention task RMS distance data, so a repeated-measures ANOVA model with natural-log transformed data was also run. There was still no evidence for a time by condition interaction (Greenhouse–Geisser adjusted $P = 0.45$) and no overall difference between conditions (Greenhouse–Geisser adjusted $P = 0.46$), so no further comparisons were made.

infusion phase when isoflurane administration was ongoing. By contrast, BIS levels after termination of anesthesia recovered more rapidly when caffeine was administered. Emergence, as defined by gagging, occurred at an average BIS value of 62. Significance was determined with a repeated-measures ANOVA (see "Materials and Methods").

Table 2 shows minute ventilation after terminating isoflurane and at emergence. Immediately after terminating isoflurane, minute ventilation showed a modest but statistically significant increase in the presence of caffeine as compared to saline. If a single data point corresponding to a participant who experienced an unusually large increase in minute ventilation when receiving caffeine is removed, the difference is no longer significant. Table 2 also demonstrates no significant change in mean arterial pressure or heart rate during or after caffeine infusion and no statistically significant difference in these vital signs when comparing caffeine to saline.

Figure 3 compiles data obtained from psychomotor testing. Only one saline-infused subject was able to complete psychomotor testing at 15 min after emergence, as compared to five who were able to do so after caffeine administration (table 1). Figure 3, A and B, shows no statistically significant difference in visual analog scale assessment of whether participants felt good or bad between caffeine and saline sessions. In the Sternberg test of memory participants

Table 1. Time to Emergence, Emergence End-tidal Isoflurane Concentration, and Number of Subjects Completing Psychomotor Testing at 15 min during Saline and Caffeine Sessions

Endpoint	Saline	Caffeine
Time to emergence, min (mean ± SD)	16.5 ± 3.9	9.6 ± 5.1
End-tidal isoflurane at emergence, % (mean ± SD)	0.21 ± 0.01	0.33 ± 0.03
Number of test subjects able to complete psychomotor testing at 15 min	1	5

Table 2. Minute Ventilation, Blood Pressure, and Heart Rate before and after Caffeine or Saline Infusion

Vital Sign	Saline	Caffeine
Minute ventilation, l/min (mean ± SD)		
Postinfusion	6.2 ± 1.4	7.2 ± 1.1
Emergence	7.5 ± 2.1	8.5 ± 3.7
Mean arterial pressure, mmHg (mean ± SD)		
Preanesthesia	89 ± 9	90 ± 7
5 min after anesthesia	72 ± 9	79 ± 15
30 min after anesthesia	94 ± 10	98 ± 3
60 min after anesthesia	96 ± 6	98 ± 2
Heart rate, beats/min (mean ± SD)		
Preanesthesia	79 ± 13	75 ± 11
5 min after anesthesia	71 ± 16	66 ± 10
30 min after anesthesia	79 ± 7	75 ± 9
60 min after anesthesia	67 ± 6	67 ± 9

performed equivalently well when they received saline or caffeine with respect to correct response rate (data not shown), and the decreased response latency (fig. 3C) when they received caffeine was not statistically significant (P = 0.64). Figure 3D plots the root-mean-squared deviation from the ideal flight path recorded in the divided attention task flight simulation exercise normalized to values obtained during the preanesthetic test training sessions. The small improvement in performance with caffeine administration was not statistically significant (P = 0.18). It will require a larger study population to determine whether there are differences in psychomotor recovery times or whether there are none. No test subjects reported any adverse effects either during recovery or throughout a 1-week follow-up period.

Discussion

In this study, we demonstrate that caffeine actively accelerates emergence from isoflurane anesthesia in human volunteers and speeds restoration of psychomotor function without any negative effects, extending our previous findings that caffeine dramatically accelerates emergence from isoflurane anesthesia in rats. The 42% acceleration of emergence with caffeine that we report herein is consistent with the approximately 50% acceleration predicted (derived from fig. 6 in the article by Wang *et al.*[16]) from our rat experiments. Small differences in emergence were observed among different groups of rats,[16] but there may be species differences as well.

Various lines of evidence suggest that the acceleration of emergence we observe represents an active effect of caffeine rather than merely a pharmacokinetic artifact of inhaled anesthetic elimination. Whereas our data do show modestly increased postinfusion minute ventilation after caffeine administration (table 2), this difference does not persist with the exclusion of one outlying data point corresponding to a single subject who experienced a four-fold increase in minute ventilation during the session in which he received caffeine. Subjects awoke, on average and each individually, at a significantly higher expired concentration of isoflurane when receiving caffeine as compared to saline (0.33 *vs.* 0.21%; table 1), indicating that caffeine promotes emergence with higher levels of isoflurane still present. The recovery of consciousness after anesthesia was significantly faster when subjects were treated with caffeine than with saline (fig. 2C). This rapid recovery of consciousness may have a short-term effect on the performance of cognitive function tests, but its long-term impact remains to be characterized.

Caffeine is the most commonly used psychoactive drug, a stimulant that is ingested daily by more than 90% of adults in the United States. Clinically, it is used to treat neonatal apnea (at per kilogram doses higher than that employed in this study) and certain types of headache. Caffeine acts by a variety of mechanisms including inhibiting phosphodiesterase to elevate intracellular cAMP, as well as antagonizing adenosine receptors A_1 and A_{2A}. Blockade of the A_{2A} receptor subtype has been shown to mediate caffeine's arousal effects.[21] We have shown recently that the ability of caffeine to accelerate emergence from anesthesia in rats depends both on its ability to antagonize adenosine receptors and its capacity to elevate intracellular cAMP.[22]

Psychomotor impairment can persist for hours after emergence from anesthesia. Postoperative delirium and prolonged recovery can engender significant morbidity and increased healthcare costs. Several studies have probed psychomotor recovery from anesthesia. For instance, 30 min after sevoflurane anesthesia, subjects performed as well on a digital substitution test as those with a 0.1% blood alcohol level.[23] In another study, 26% of patients were unable to complete a digital substitution test 2 h after termination of either sevoflurane or desflurane anesthesia, even though average eye opening and extubation occurred within 10 min.[24] Elderly patients represent a particularly vulnerable population in which cognitive abilities can remain impaired hours after anesthesia.[3] Even subanesthetic doses of sevoflurane cause significant cognitive impairment.[25,26]

Our results did not show a significant difference in speeding recovery of psychomotor function when subjects were given caffeine. Nonetheless, five of eight subjects were able to participate in psychomotor testing at 15 min postemergence when they were given caffeine as opposed to only one of eight when they were given saline (table 1). There was a large variance in the psychomotor data and a small sample size. A larger cohort of volunteers will be required to determine whether caffeine accelerates recovery of cognitive function

after anesthesia. Finally, seven of our eight participants were students in rigorous academic disciplines for whom the Sternberg test of memory seemed facile, and this is likely to have obscured differences that would be apparent in the general population. Although future studies are needed to better resolve the effects of caffeine on the restoration of psychomotor function after anesthesia, these initial data at least leave open the possibility that caffeine enhances recovery.

We observed no adverse effects in our healthy male volunteers that were attributable to caffeine at the dosage we administered (equivalent to the amount of caffeine in two large cups of coffee for a 70-kg individual). Blood pressure and heart rate were unchanged by caffeine both during the infusion period and throughout the subsequent recovery phase (table 2) and were indistinguishable between caffeine and saline sessions. Assessment in both the immediate recovery phase and for 1 week after each anesthetizing session yielded no reports of adverse effects and no difference in any subject complaints between caffeine and saline sessions. We conclude from this that caffeine is safe and efficacious in healthy males at the dosage employed in this study.

There have been other attempts to reverse anesthesia in humans. For example, physostigmine, a cholinesterase inhibitor, has been shown previously to reverse postoperative somnolence[27] and propofol sedation,[28] although was less reliable when used with the volatile anesthetic sevoflurane.[29] Several studies have used aminophylline to accelerate recovery from anesthesia in human test subjects.[8–10,30–32] Aminophylline is composed of theophylline and ethylenediamine; the latter moiety added to enhance aqueous solubility. Although aminophylline produced a robust acceleration in emergence from anesthesia and in recovery of cognitive abilities after terminating anesthesia, several studies observed a significantly increased heart rate in response to the drug. In our rodent studies, we never tested aminophylline, but we did test the active component, theophylline; caffeine was more effective at accelerating emergence from anesthesia than was theophylline. Two human trials have been initiated using methylphenidate as a potential anesthesia reversal agent: one led by Ken Solt, M.D., at Massachusetts General Hospital (ClinicalTrials.gov identifier NCT02051452) and the other lead by Nicoleta Stocicea, M.D., Ph.D., at Ohio State University (ClinicalTrials.gov identifier NCT62327195). Methylphenidate may realize its promise as another anesthesia reversal agent, although its status as a Schedule II drug with a less favorable risk profile might limit its widespread utility.

The clinical promise of caffeine as a potential reversal agent for general anesthesia lies not primarily in its routine use to accelerate emergence in every patient, because anesthesia providers routinely control emergence time simply by their choice of when to discontinue the administration of the anesthetizing agent. Rather, the judicious use of caffeine could provide a tool to accelerate emergence in those individuals who manifest unanticipated prolonged emergence times and populations, such as the elderly, that are prone to prolonged emergence and recovery. Realizing this promise will require validation of efficacy and safety in larger clinical studies. Further work is needed, and will follow, to extend these findings to other anesthetics including common IV agents like propofol, as well as demonstrating that these results are reproducible in patient populations, including females, older individuals, and those with chronic medical conditions undergoing operative procedures who receive multiple classes of pharmacologic agents in the course of a normal anesthetic. This study represents a necessary and promising first step in the development of this pharmacologic strategy.

Beyond its potential clinical implications, the results of this study encourage further basic investigation into the mechanistic basis of general anesthesia. Specifically, the results of our previous work in rats established a potential role for modulation of intracellular cAMP in maintaining the anesthetic state. The observation in this study that caffeine accelerates emergence in human subjects as robustly as it does in rats suggests a generalizability of this mechanistic paradigm and promises that insights gained from future studies in animal models to further characterize this mechanistic link would likely be applicable to understanding anesthetic action in people.

Conclusions

We have shown that caffeine is an effective way to actively reverse isoflurane anesthesia in healthy male volunteers. No adverse effects of caffeine were observed, raising the possibility that the procedure is safe, but a larger sample size with a broader patient population will be required to unequivocally establish this point. Further investigation with larger sample sizes and more robust testing methodologies will be needed to establish whether caffeine enhances psychomotor recovery.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: jxie@dacc.uchicago.edu. Raw data available at: jxie@dacc.uchicago.edu.

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Appendix: Statistical Calculation

There were no human data for estimating the number of test subjects to use. We used our own data from rats to provide guidance.

Why expose test subjects to two rounds of isoflurane anesthesia, once with caffeine and once without? How many human subjects will be required? There were several reasons why our sample size might be in error. First, rats are not people. They may get rid of isoflurane differently than do humans. In addition, rats are genetically more similar to each other than are humans. That would tend to increase human variance relative to rat. On the other hand, the equipment used to anesthetize rats is less sophisticated than that in humans. In humans, the expired anesthetic concentration is measured, thereby allowing for precise anesthetic concentration, in the lungs. This will tend to lower human variance. In our studies, rats were used four times (twice with a saline injection and twice with an injection of saline containing caffeine). This will increase variance in humans.

The statistical information came from experiments already completed.[16] We use the following stringent criteria to determine sample size (power will be set to 95% and $P \leq 0.01$).

Rats waking from isoflurane anesthesia with 5 mg/kg caffeine:

Control – saline injection	mean = 540 s, SD = 159.04
Test – 5 mg/kg caffeine in saline injection	mean = 269.67 s, SD = 103.69

At this concentration of caffeine, we would need n = 12 measurements for control and n = 12 measurements for caffeine to meet our stated stringent criteria.

Rats waking from isoflurane anesthesia with 25 mg/kg caffeine:

Control – saline injection	mean = 477.32 s, SD = 146.32
Test – 25 mg/kg caffeine in saline injection	mean = 191.25 s, SD = 103.69

We would need n = 7 measurements for control and n = 7 measurements for caffeine to meet our stated criteria.

The caffeine formulation and concentration used in the current study was 15 mg/kg caffeine citrate. This is equivalent to 7.5 mg/kg of caffeine base, which was used in the rat study. Therefore we would require fewer test subjects than the 5 mg/kg data shown above but more than that for 25 mg/kg. In addition, the 7.5 mg/kg was located at a steep part of the caffeine dose–response curve but not close to the EC_{50} value. The 25 mg/kg was near saturation of the dose–response curve. Our best estimate from the data shown above and the dose–response curve shown by Wang *et al.*[16] is that we would require n = ~10 test subjects for a concentration of 7.5 mg/kg caffeine.

However, another adjustment needed to be made. The rats were tested at ~1.5 minimum alveolar concentration of isoflurane, whereas the human volunteers were tested at 1 minimum alveolar concentration. The lower isoflurane concentration should be easier for caffeine to antagonize and will require fewer test subjects. Although just an estimate, we hypothesized that n = 8 test subjects, with each subject tested twice, would be sufficient to answer the question of whether caffeine could accelerate emergence from anesthesia.

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