Chronic Cocaine Administration Reversibly Increases Isoflurane Minimum Alveolar Concentration in Sheep

Christopher M. Bernards, M.D.,* Christian Kern, M.D.,† Bruce F. Cullen, M.D.‡

Background: Significant numbers of patients are seen for surgery and anesthesia with a history of chronic cocaine use. However, little is known about how cocaine use influences anesthetic physiology and pharmacology. The purpose of this study was to investigate the effect of chronic cocaine exposure on the minimum alveolar concentration (MAC) of isoflurane in sheep.

Methods: Isoflurane MAC was determined at baseline in 12 sheep using a standard protocol. The animals were subsequently exposed to cocaine for 18 days. Cocaine exposure consisted of a continuous subcutaneous cocaine infusion at 0.2 mg·kg⁻¹·h⁻¹, twice daily 4 mg/kg intravenous boluses and repeated hourly 4 mg/kg cocaine boluses for 8 h on day 18. Minimum alveolar concentration determinations were repeated again on days 15, 18, and on day 28 after 10 days of cocaine abstinence.

Results: Compared to baseline MAC (1.53 ± 0.12%) cocaine exposure significantly increased isoflurane MAC on days 15 (1.91 ± 0.14%) and 18 (1.78 ± 0.13%; P = .005). MAC decreased after discontinuation of cocaine and was not different from baseline on day 28 (1.67 ± 0.11).

Conclusions: In sheep, chronic cocaine exposure resulted in a reversible increase in isoflurane MAC. This finding contrasts with studies of other central nervous system stimulants, which have demonstrated a decrease in MAC after chronic drug exposure. (Key words: Anesthetics, inhalational; isoflurane. Anesthetics, narcotic; cocaine. Animals: sheep. Potency, anesthetic: minimum alveolar concentration.)

COCAIN is one of the most widely abused drugs in the United States with 25–40 million Americans admitting to having used it and upwards of 3.5 million who admit to being regular users.§ In addition, cocaine has increasingly been associated with both blunt and penetrating trauma. As a result, an increasing number of patients are seen for surgery and anesthesia with a history of cocaine use. Yet, very little is known about how cocaine use affects anesthetic physiology and pharmacology. In particular, the effect of cocaine on anesthetic requirement is poorly understood.

Animal studies indicate that acute cocaine ingestion increases halothane minimum alveolar concentration (MAC) and experience with acute cocaine intoxication in humans suggests that cocaine decreases the sedative/hypnotic potency of benzodiazepines. However, many cocaine users have a history of regular cocaine use, although they may not be acutely intoxicated. Studies of other central nervous system stimulants, e.g., amphetamines, demonstrate that chronic exposure reverses the drug’s acute MAC increasing effects and results in a MAC decrease. Unfortunately, the effects of chronic cocaine use on anesthetic requirement are not known.

The purpose of this study was to determine whether chronic cocaine use alters anesthetic requirement. To do this, we used sheep to determine isoflurane MAC before, during, and after chronic cocaine exposure.
Methods

Studies were approved by the University of Washington Animal Care and Use Committee and American Association for the Accreditation of Laboratory Animal Care guidelines were followed throughout.

Twelve, farm-bred, male sheep weighing 23.3-30.5 kg were used for all studies. The animals were housed singly at the University of Washington vivarium. The animals were given ad libitum access to water and twice daily feedings of an age appropriate amount of sheep chow.

Minimum Alveolar Concentration Determination

On day 0, anesthesia was induced by mask inhalation of isoflurane in oxygen. Tracheal intubation was facilitated by intravenous injection of 30-40 mg succinylcholine. The animals’ lungs were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 36-40 mmHg. A 16-G intravenous catheter was placed in the internal jugular vein for subsequent cocaine administration.

Minimum alveolar concentration was determined as previously described by Merkel and Eger. Briefly, the supramaximal stimulus consisted of an alligator clip applied to the margin of the ear for 1 min and vigorously twisted every 10 s. The end-tidal isoflurane concentration was initially adjusted to a level at which the animals moved vigorously in response to the stimulus. In this way, we verified that the animals were no longer paralyzed by succinylcholine and were capable of responding to a painful stimulus. The isoflurane concentration was then increased to a concentration at which the animals did not move in response to the stimulus. Subsequently, the end-tidal isoflurane concentration was decreased in increments of 0.1–0.2% until the animals again moved in response to the stimulus. The end-tidal isoflurane concentration midway between the last concentration at which the animals did not move and the final concentration at which the animals did move in response to the stimulus was considered to be MAC. After any change in anesthetic delivery, end-tidal isoflurane concentration was required to be constant for at least 10 min and to differ from the inspired concentration by less than 0.1% before reapplying the supramaximal stimulus.

End-tidal isoflurane concentrations were measured with a Datex Capnomac AGM-103 gas analyzer (Datex, Helsinki, Finland). The airway gas sampling port was attached to the y-piece of the circle system.

Minimum alveolar concentration determinations were made in all animals on day 0 before cocaine exposure and on days 15 and 18 after cocaine exposure as outlined later. Minimum alveolar concentration was determined again in eight animals on day 28 after cocaine had been discontinued for 10 days.

Cocaine Administration

Cocaine was administered both by continuous subcutaneous infusion and by intermittent intravenous bolus. The continuous cocaine infusion was administered by osmotic pump (Alzet model 2ml2, Palo Alto, California). These pumps were loaded with 2 ml cocaine hydrochloride and were placed subcutaneously on the sheep’s back at the end of the first day’s study. These pumps delivered cocaine base continuously at the rate of 0.2 mg·kg⁻¹·h⁻¹. The continuous infusion pumps were used to maintain a steady low level background plasma cocaine concentration between cocaine boluses.

In addition to the continuous cocaine infusion, the animals also received 4 mg/kg intravenous cocaine boluses. The cocaine boluses were rapidly injected (1-2 s) via a catheter placed in the internal jugular vein. The cocaine boluses were administered every morning and evening of days 1-17 except day 15 when the morning bolus was omitted before the repeat MAC study on that day. The cocaine boluses were meant to mimic acute cocaine ingestion by humans. Beginning at midnight on day 18, the animals received 8 hourly cocaine boluses of 4 mg/kg to mimic a cocaine “binge.” The cocaine boluses were administered over 10 min by a miniature infusion pump worn on the animal’s back. The repeat MAC study on day 18 was performed 3 h after the last cocaine bolus.

At the end of the study on day 18, the osmotic pumps were removed and all cocaine administration was stopped.

Cocaine Plasma Assay

Venous blood (5 ml) was collected for determination of trough cocaine plasma concentrations in the morning of days 5 and 10 before the cocaine bolus and on day 15 before the repeat MAC study. Blood was withdrawn from the same line through which the cocaine was administered after the line was appropriately flushed with 20 ml normal saline. On day 18, blood was drawn 3 h after the last cocaine bolus just before beginning the repeat MAC study. All blood samples were collected into commercial tubes containing sodium fluoride to prevent cocaine me-
tabolism by plasma cholinesterase. The plasma was separated and frozen at $-20^\circ$C for later analysis.

Cocaine was assayed in the University of Washington Department of Anesthesiology analytical laboratory by a modification of the method of Bjork et al. Briefly, plasma was alkaliniized by addition of sodium hydroxide and cocaine was extracted into heptane/ethyl acetate. Cocaine was separated by gas chromatography and detected by a nitrogen-phosphorous detector. The limit of quantification was 10 ng/ml and the coefficient of variation at 1 ng/ml was 5%.

Statistical Analysis

The data were analyzed for statistical significance using repeated measures analysis of variance. Dunnett's $t$ test was used on a post hoc basis to compare MAC on days 15, 18, and 28 with baseline MAC on day 0. Differences were considered statistically significant at the $P < 0.05$ level. All data are presented as the mean ± SE.

Results

Isoflurane MAC averaged 1.53 ± 0.12% at baseline before cocaine exposure. Mac was significantly greater on days 15 (1.91 ± 0.14%), 16 (1.78 ± 0.13%; $P = 0.005$), and 18 (1.78 ± 0.13%; $P = 0.005$). On day 28, 10 days after cessation of cocaine exposure, MAC decreased to 1.67 ± 0.11%, which was not significantly different than baseline MAC. Figure 1 shows the values for isoflurane MAC for each animal on each experimental day.

Trough cocaine plasma concentrations averaged 68.8 ± 19 ng/ml on day 5, 35.8 ± 11 ng/ml on day 10, 15.2 ± 4.2 ng/ml on day 15, and 46.0 ± 29.5 ng/ml on day 18. There were no statistically significant differences in cocaine plasma concentrations among the sample days ($P = 0.352$).

Discussion

Baseline isoflurane MAC in these young sheep (1.53%) was nearly identical to that previously reported by Brett et al. (1.51%). The subsequent reversible increase in MAC after chronic cocaine exposure contrasts with the findings of an earlier study by Stoelting et al. These investigators found that acute cocaine exposure increased halothane MAC in dogs but that "chronic" exposure did not alter MAC from baseline. The reasons for the disparate findings between our two studies are not clear but species differences and that Stoelting et al. studied only two animals are possible explanations. Perhaps a more likely explanation is that Stoelting et al. used a shorter duration of cocaine exposure (9 days vs. 14 and 18 days in the current study) and a lower frequency of exposure (once daily boluses vs. twice daily boluses and a continuous background infusion in the current study). Thus, greater cocaine exposure may explain the conflicting findings of the current study and the earlier study by Stoelting et al.

![Fig. 1. Isoflurane minimum alveolar concentration for each animal on day 0 before cocaine exposure, on days 15 and 18 after chronic cocaine exposure, and on day 28 after 10 days of cocaine abstinence. *P < 0.05 compared to day 0.](image-url)
Our finding of an increase in MAC with chronic cocaine exposure conflicts with studies demonstrating that amphetamines, also central nervous system stimulants, decrease MAC with chronic exposure. The ability of chronic amphetamine exposure to decrease MAC is thought to be related to depletion of adrenergic neurotransmitters in the brain. However, chronic cocaine administration has been shown not to decrease regional brain concentrations of norepinephrine. In fact, several animal models of cocaine abuse demonstrate that chronic cocaine exposure increases adrenergic activity. Seidler and Slotkin have shown that chronic cocaine exposure results in noradrenergic hyperactivity in the midbrain, brain stem, forebrain, and cerebellum of fetal rats. Similarly, Kelley et al. have shown that chronic cocaine exposure results in significant increases in plasma norepinephrine and epinephrine concentrations in response to exercise. These studies suggest that chronic cocaine exposure does not down-regulate adrenergic systems, rather noradrenergic activity is actually increased in some systems by chronic cocaine exposure. These effects of chronic cocaine on adrenergic systems may help explain the ability of chronic cocaine exposure to increase MAC.

Alternatively, cocaine could conceivably increase MAC by diminishing the activity of inhibitory neurotransmitter systems. In contrast to adrenergic neurotransmitters, chronic cocaine exposure does result in decreased dopaminergic, and GABAergic activity in some brain regions. Because these neurotransmitters are generally inhibitory, reduction in their activity might result in increased anesthetic requirements.

All animals had low but detectable plasma concentrations of cocaine at the time that MAC was measured on days 15 and 18. This was intentional, because we wanted to mimic the situation of a person who uses cocaine with sufficient frequency that they are nearly always exposed to some concentration of the drug. Based on human population kinetics for cocaine elimination, we estimate that the average plasma concentration of cocaine at the time of MAC determination is similar to that which would be present in a human approximately 2–3 h after consuming a cocaine dose that has been shown to produce “typical” subjective effects in regular cocaine users. This represents 1 or 2 h after all subjective effects of cocaine have been shown to subside in humans. There was no correlation between the measured MAC value in individual animals and their plasma cocaine concentrations. Thus, we do not think that the increase in MAC on days 15 and 18 of our study was the result of acute cocaine intoxication. Finally, Johnston et al. report that dextroamphetamine concentrations in the plasma of their chronically exposed dogs ranged between 9.5 and 113.5 ng/ml at the time of MAC determination. Despite the continued presence of amphetamine in these animals, the investigators were still able to detect a significant decrease in MAC with chronic amphetamine administration. Thus, the methodological similarity between our two studies further supports our observation that the effects of chronic cocaine exposure and chronic amphetamine exposure on MAC are in fact very different.

Our study was designed to address a relevant clinical question—does chronic cocaine use alter anesthetic requirement in patients undergoing surgery and anesthesia? We chose to answer this clinical question in an animal model because of the obvious difficulties in conducting a controlled study of drug use in humans. Unfortunately, there are no animals that metabolize cocaine exactly as do humans, nor that respond pharmacodynamically to cocaine exactly as do humans. Perhaps the principal pharmacokinetic difference between rats and humans is more rapid clearance of cocaine in sheep resulting in a significantly shorter plasma half-life (9.34 ± 0.79 min in sheep vs. 48 ± 13 min in humans). Because of more rapid elimination, a given cocaine dose will result in significantly less cocaine exposure in sheep than in humans. Consequently, we chose a cocaine bolus dose (4 mg/kg) that was several times greater than intravenous doses that have been shown to produce typical “highs” in regular cocaine users (approximately 0.3–0.6 mg/kg). In addition, we added a continuous background cocaine infusion so that animals would always have some exposure to cocaine. In this way we hoped to mimic the “heavy” cocaine user who uses the drug with sufficient frequency that they never completely clear the drug from their plasma before their next dose.

We also sought to mimic a representative pattern of cocaine consumption. However, this was essentially impossible because there is no “typical” pattern of human cocaine use. Human consumption patterns vary from rare to chronic habitual use to binges lasting hours or days. As discussed earlier, we think that the pattern of daily cocaine administration is representative of people who consume cocaine repeatedly throughout the day. The repeated hourly cocaine boluses administered before the study on day 18 were designed to

References
1. Stearns PM, Tarafid K, Leon
2. Barnett N, Iqbal M. Fatal iapone
3. Brookes DF, Campbell E, Stark
4. Scott LM, Creaser CM, Mar
5. Bernards C, Tejepkraj A: Ilee
7. Nielson G, Tager EL. A com
8. Bjork M, Peterson K, Oster
9. Anesthesiology, V 85, No 1, Jul 1996
10. Anesthesiology, V 85, No 1, Jul 1996
mimic a cocaine binge, which is a common use pattern in humans.

In summary, we used a sheep model of chronic cocaine use to demonstrate that chronic cocaine exposure reversibly increases isoflurane MAC. This finding suggests that heavy cocaine use in humans also increases isoflurane MAC.

References