Laboratory Investigations

Chronic cocaine administration does not modify haemodynamic responses to isoflurane anaesthesia in sheep

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Purpose: Cocaine use is epidemic in the developed world, resulting in numerous patients presenting for surgery and anaesthesia with a history of chronic cocaine exposure. The purpose of this study was to determine the effect of chronic cocaine exposure on the cardiovascular response to isoflurane general anaesthesia.

Methods: The changes in mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) with increasing concentration of isoflurane (1%, 1.7%, and 2.4% end tidal) were determined at baseline in six sheep. The animals then received a continuous cocaine infusion (0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$) and twice daily cocaine boluses (4 $mg \cdot kg^{-1}$) for 17 days followed on day 18 by a cocaine binge consisting of eight cocaine boluses (4 $mg \cdot kg^{-1}$) administered at one hour intervals. The haemodynamic studies conducted at baseline prior to cocaine exposure were then repeated on days 15 and 18.

Results: Increasing concentrations of isoflurane produced the expected dose-dependent cardiovascular depression, but this was not altered by cocaine exposure.

Conclusion: Although chronic cocaine exposure has been shown to increase isoflurane minimum alveolar concentration by 25% in sheep; chronic cocaine exposure does not result in tolerance of the cardiovascular depression produced by isoflurane.

Objectif : Dans les pays industrialisés, l'abus de la cocaïne a maintenant atteint l'état épidémique. De nombreux patients arrivent maintenant en anesthésie et en chirurgie avec une histoire de toxicocomanie. Cette étude visait à déterminer les effets de l'exposition chronique à la cocaïne sur la réponse cardiovasculaire de l'anesthésie générale à l'isoflurane.

Méthodes : Les changements produits sur la pression artérielle moyenne, la fréquence cardiaque, le débit cardiaque, la tension veineuse centrale, la pression capillaire bloquée et la résistance vasculaire systémique par des concentrations croissantes d'isoflurane (télé-expiratoires 1%, 1,7% et 2,4%) ont d'abord été déterminés sur six moutons. Les animaux ont ensuite reçu une perfusion continue (0,2 $mg \cdot kg^{-1} \cdot h^{-1}$) et deux bolus quotidiens (4 $mg \cdot kg^{-1}$) de cocaïne pendant 17 jours, suivis, le 18e jour, par une série de huit bolus (4 $mg \cdot kg^{-1}$) administrés à une heure d'intervalle. Les études hémodynamiques ayant servi comme valeurs de base avant l'exposition à la cocaïne ont ensuite été répétées le 15e et le 18e jour.

Résultats : L'augmentation de la concentration d'isoflurane a provoqué la dépression cardiovasculaire proportionnelle prévue sans modification par la cocaïne.

Conclusion : Bien qu'il ait été démontré que l'exposition chronique à la cocaïne augmente la concentration alvéolaire minimum de 25% chez le mouton, elle n'augmente pas la tolérance à la dépression cardiovaculaire produite par l'isoflurane.

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COCAINE use is epidemic throughout much of the world, resulting in an increasing number of patients presenting for surgery and anaesthesia with a history of chronic cocaine exposure. This is especially true of patients presenting for emergency surgery and anaesthesia following either blunt or penetrating trauma.[1–3] Unfortunately, little is known about how chronic cocaine use affects the physiological and pharmacological response to anesthesia. Consequently, clinicians are left to wonder whether they should alter their usual anaesthetic practice when caring for these patients.

We have previously demonstrated that chronic cocaine exposure reversibly increases isoflurane minimum alveolar concentration (MAC) by 25% in sheep.[4] Thus, patients with a history of chronic cocaine use are likely to require greater concentrations of volatile anaesthetics to assure an appropriate anaesthetic depth. However, it is not known how well cocaine using patients are able to tolerate the greater cardiovascular depression that accompanies higher concentrations of volatile anaesthetics.[5]

Chronic cocaine exposure has been shown to impair autonomic activity in animal models. Studies in rats demonstrated that as few as seven days of chronic cocaine exposure reduced the responsiveness of adrenergic receptors in the peripheral sympathetic nervous system, presumably because of receptor down-regulation.[6] In addition, isoflurane has been shown to decrease efferent sympathetic nervous system activity.[7–9] Thus, the ability of these two drugs to impair sympathetic nervous system activity at two separate sites may put cocaine abusing patients at greater risk for cardiovascular compromise during anaesthesia with volatile anaesthetics.

The purpose of this study was to determine if chronic cocaine use alters the cardiovascular response to general anesthesia. To address this question, we employed a sheep model of chronic cocaine exposure which attempts to mimic both daily cocaine use and cocaine "binges," a common cocaine use pattern in humans.[10] We used this model to investigate the effect of chronic cocaine exposure on the cardiovascular responses to varying depths of isoflurane general anesthesia.

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.

Six male, farm-bred, sheep weighing 21–24.5 kg were used for all studies. The animals were housed singly at the University of Washington vivarium and were given *ad lib* access to water and twice daily feedings of an age appropriate amount of sheep chow.

Animal Instrumentation

On all study days, the animals were brought to the laboratory in the morning and anaesthetized by mask inhalation of isoflurane (2–4%) in oxygen. They were paralyzed with succinylcholine (20–40 mg *iv*), their trachea's were intubated and their lungs were ventilated mechanically to maintain P_{ET} CO_2 at 34–40 mm Hg. Anaesthesia was maintained with isoflurane (1.5–2.0% end-tidal) in oxygen. Temperature was kept between 37.5°C and 38.5°C by servo-controlled heat lamps and a rectal temperature probe.

A pulmonary artery catheter introducer (Arrow International, Inc.) was placed in the right internal jugular vein and a pulmonary artery catheter (American Edwards) was positioned in the pulmonary artery. An 18G or 20G arterial cannula was placed in an artery of the right or left distal foreleg via a cutdown. The skin around the arterial cannula insertion site and the pulmonary artery catheter insertion site was infiltrated with a total of 3–4 ml plain bupivacaine 0.25%. Sterile needle electrodes were inserted subcutaneously at the right and left shoulders and the left flank in order to monitor lead II of the ECG.

Following placement of the haemodynamic monitors, the animals were suspended in a body sling with their heads held upright. The anaesthetic was then discontinued and the animals were allowed to recover for one hour after their trachea's were extubated. During the recovery period the animals were given 10 $ml \cdot kg^{-1}$ lactated Ringer's solution *iv*.

Study Paradigm

One hour after extubation, baseline mean arterial pressure (MAP), cardiac output (CO) in triplicate, heart rate (HR), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were determined in the awake animals. The animals were then re-anaesthetized by inhalation of isoflurane via face mask. The animals were then paralyzed with succinylcholine (40–60 mg *iv*), their trachea's were intubated and their lungs were ventilated mechanically with approximately 60% oxygen and 40% nitrogen to maintain $P_{ET}CO_2$ at 38–40 mm Hg. Arterial blood gases were measured (Corning model 170 pH/Blood Gas Analyzer, Ciba Corning Diagnostics Corporation, Pleasanton, California) to verify that $P_{ET}CO_2$ accurately reflected arterial P_aCO_2. Following induction of anaesthesia, the expired isoflurane concentration was equilibrated at 2.4% and the haemodynamic measurements repeated. The expired isoflurane concentration was then decreased sequentially to 1.7% and finally 1.0% and haemodynamic measurements repeated at each concentration. Isoflurane concentration was determined by infra-red spectroscopy (Datex model

254 Airway Gas Analyzer, Datex Inc., Helsinki, Finland) and was required to be stable at the target expired concentration for at least 20 min before haemodynamic measurements were made. At the completion of each day's study, the arterial cannula and the pulmonary artery catheter were removed although the pulmonary artery catheter introducer was left in place for subsequent cocaine administration.

This study paradigm was performed at baseline (day 0) before cocaine exposure and again on days 15 and 18 following cocaine exposure as outlined below.

Cocaine Administration

The animals received a continuous cocaine infusion at a dose of 0.2 $mg \cdot kg^{-1} \cdot hr^{1}$ and twice daily cocaine boluses of 4 $mg \cdot kg^{-1}$ *iv* for 17 consecutive days following the baseline haemodynamic measurements. The cocaine boluses were meant to mimic the rapid and large variations in cocaine plasma concentration which accompany acute cocaine ingestion in humans. The background continuous infusion was designed to maintain a low concentration of cocaine continuously in the animals' plasma. In this way it was hoped to mimic a patient who uses cocaine with sufficient frequency that they never completely clear the drug or its active metabolites from their plasma. On day 18, the animals received eight consecutive 4 $mg \cdot kg^{-1}$ cocaine boluses at hourly intervals before the final haemodynamic study. This was meant to mimic a cocaine "binge" which is a common pattern of cocaine use in humans.[10] The timing and methods of drug administration are described below.

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 continuously at the rate of 0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$. The initial pumps were replaced with fresh pumps at the end of the study on day 15.

The animals also received twice daily 4 $mg \cdot kg^{-1}$ cocaine boluses *iv*. The cocaine boluses were rapidly injected (one to two seconds) via the pulmonary catheter introducer in the morning and evening of days 1–17. The morning cocaine bolus was omitted on day 15 before the repeat haemodynamic study.

Beginning at midnight on day 18, the animals received 4 $mg \cdot kg^{-1}$ cocaine boluses *iv* each hour for eight consecutive hours. These cocaine boluses were administered over 10 min by a miniature infusion pump (CADD-Plus, Pharmacia Deltec Inc., St. Paul, MN) worn on the animals' back. Haemodynamic measurements began three hours after the last cocaine bolus.

Statistical Analysis

Repeated measures analysis of variance (ANOVA) was used to determine whether the haemodynamic responses to increasing concentrations of isoflurane were different on days 15 and 18 following cocaine exposure compared to baseline on day 0. Differences were considered significant at the $P < 0.05$ level and values are reported as the mean ± SE.

Results

Isoflurane produced dose dependent decreases in MAP (Figure 1) and CO (Figure 2) but cocaine exposure had no effect on the response of either of these variables to

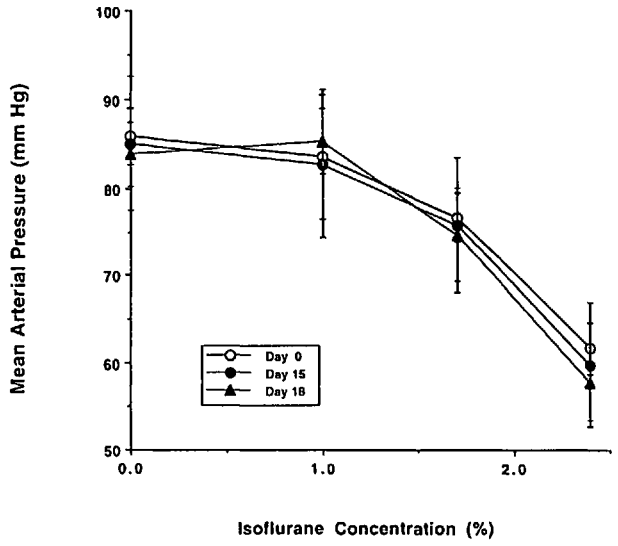
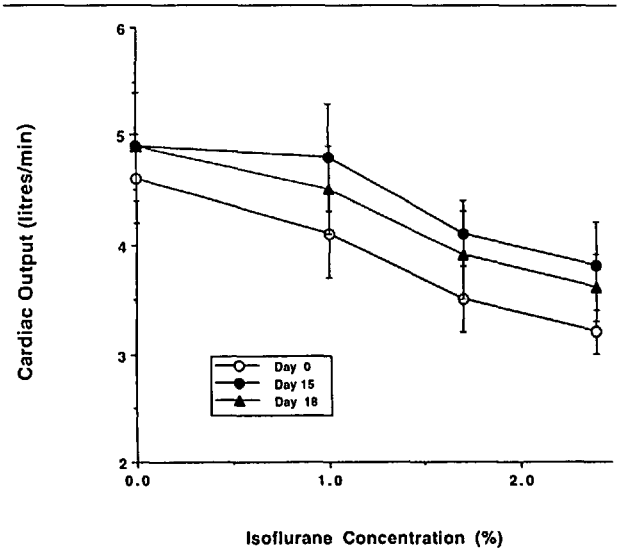


FIGURE 1



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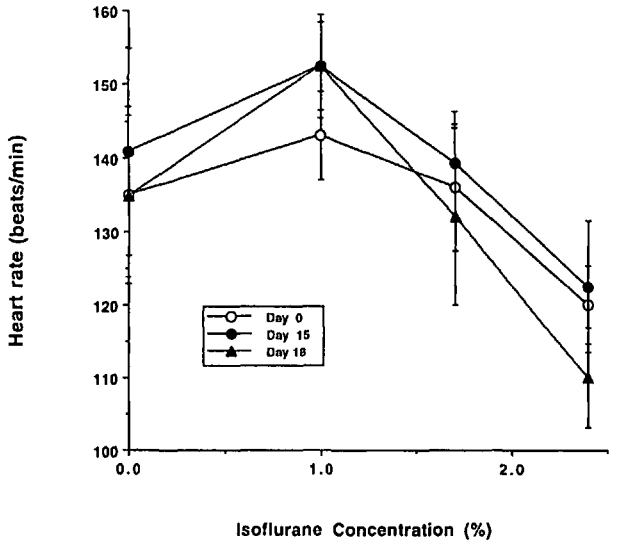

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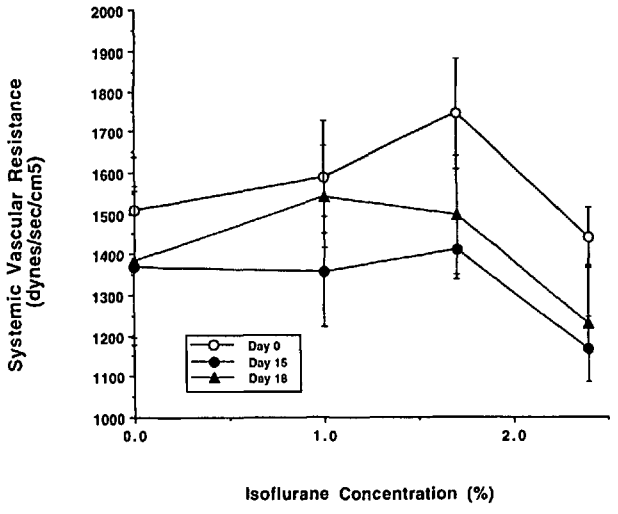

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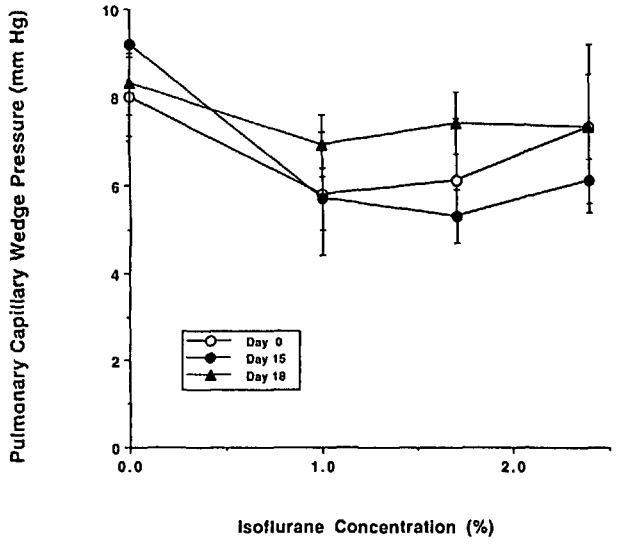

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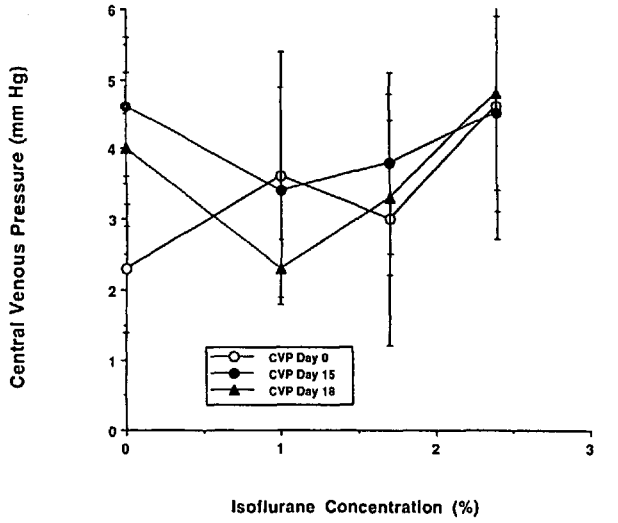

FIGURE 6

isoflurane. Heart rate (Figure 3) and SVR (Figure 4) increased at low concentrations of isoflurane and then decreased at higher concentrations, but, the response was not affected by cocaine exposure. Similarly, PCWP (Figure 5) and CVP (Figure 6) showed dose dependent changes in response to increasing concentrations of isoflurane, but, cocaine exposure did not affect the response of these variables to isoflurane.

Discussion

Since the minimum alveolar concentration (MAC) of isoflurane in sheep this age is 1.5%,[4,11] the isoflurane doses studied represent clinically relevant depths of anaesthesia 0(0.67–1.6 MAC).[12] As expected, isoflurane produced dose dependent cardiovascular depression which was manifest as decreasing MAP, CO, and HR with increasing anaesthetic depth. The decrease in MAP, CO and HR is caused by isoflurane's ability to decrease contractility[13] and to inhibit efferent sympathetic nervous system activity.[7–9] Though isoflurane inhibits sympathetic nervous system activity, residual sympathetic stimulation partially compensates for the decreased contractility.[14] The fact that chronic cocaine exposure did not have a clinically significant effect on the haemodynamic response to isoflurane suggests that cocaine did not impair the sympathetic nervous system

sufficiently to prevent this partial compensation for isoflurane-mediated depression of contractility. Whether different volatile agents might produce different results is not clear from the data.

We chose to conduct this study in an animal model because of the obvious difficulty with conducting a controlled study of drug use in humans. Unfortunately, there are no animals which metabolize cocaine exactly as do humans, nor which respond pharmacodynamically to cocaine exactly as do humans. The principal pharmacokinetic difference between sheep and humans is more rapid cocaine clearance by sheep resulting in a shorter plasma half-life (10.34 ± 0.79 min. in sheep vs 48 ± 13 min. in humans).[15,16] Because of more rapid elimination, a given cocaine dose will result in less cocaine exposure in sheep than in humans. Consequently, we chose a cocaine bolus dose (4 $mg \cdot kg^{-1}$) which was several times greater than intravenous doses which have been shown to produce typical "highs" in experienced cocaine users (0.3–0.6 $mg \cdot kg^{-1}$).[17,18]

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 varies from rare cocaine use, to habitual daily use, to binges lasting hours or days. We designed our daily cocaine bolus and continuous background infusion regimen to be representative of people who consume cocaine repeatedly throughout the day and therefore never completely clear the drug from their plasma. The repeated hourly cocaine boluses administered before the study on day 18 were designed to mimic a cocaine binge which is a another common cocaine use pattern in humans. Thus, while the cocaine regimen used in this study cannot be said to be equivalent to typical human use, we consider that it represents what one might find in compulsive cocaine users.[10]

The continuous infusion arm of the cocaine administration regimen was included to insure that all animals had some cocaine and cocaine metabolites in their plasma at all times. Although cocaine plasma concentrations were not measured in these animals, they were measured in similarly sized sheep receiving the exact same cocaine regime. In this earlier study, cocaine trough concentrations on days 5, 10 and 15 averaged 69 ± 19 $ng \cdot ml^{-1}$, 34 ± 11 $ng \cdot ml^{-1}$, and 15 ± 4 $ng \cdot ml^{-1}$ respectively and three hours after the cocaine binge on day 18 averaged 46 ± 30 $ng \cdot ml^{-1}$. There were no differences in these plasma concentrations. The low cocaine concentrations present are comparable with what one would expect to find in the plasma of humans approximately two to three hours after ingesting a dose of cocaine which produces a typical "high" in experienced cocaine users.[19] In humans, this concentration of cocaine is not associated with any cardiovascular effects, thus we do not think the presence of cocaine in the animals' plasma at the time haemodynamic measurements were made affected the results.

In summary, we used a sheep model to investigate the effects of chronic cocaine use on the cardiovascular response to isoflurane general anesthesia. We found that chronic cocaine exposure did not alter the cardiovascular response to varying concentrations of isoflurane. Thus, despite the fact that cocaine abusing patients may require greater concentrations of volatile anaesthetics, the data from this study suggest that they are not better able to tolerate the greater cardiovascular depression which accompanies higher volatile anaesthetic concentrations. This is analogous to the situation with chronic alcohol use which results in increased volatile anaesthetic requirements[20–22] but does not alter the cardiovascular depression produced by volatile anaesthetics.[22]

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