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Self-Administration of Codeine Plus Acetylsalicylic Acid in Rhesus Monkeys with Unlimited Access to the Drugs

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HOFFMEISTER, F. *Self-administration of codeine plus acetylsalicylic acid in rhesus monkeys with unlimited access to the drugs.* PHARMAC. BIOCHEM. BEHAV. 6(2) 179–182, 1977. – The reinforcing effects of codeine (5.0 mcg/kg/infusion), acetylsalicylic acid (ASA) (2500 mcg/kg/infusion) and those of combinations of codeine (50 mcg/kg/infusion) plus ASA (2500 or 10,000 mcg/kg/infusion) were studied in four groups of drug naive rhesus monkeys. Responding was engendered and maintained by infusions of 50 mcg/kg of codeine; maximal number of daily infusions being 500 to 1000. Infusions of 2500 mcg/kg of ASA failed to initiate and maintain responding during a 14 day drug period. A combination of 2500 mcg/kg of ASA plus 50 mcg/kg of codeine per infusion initiated responding from the 9th to the 10th day of the drug period on. The number of self-administered infusions did not exceed 200 daily. Monkeys self administered codeine without signs of intoxication. All three monkeys self-administering the combination of 50 mcg/kg of codeine plus 2500 mcg/kg of ASA died during the experiment. They exhibited signs of severe intoxication. A combination of 50 mcg/kg of codeine and 10,000 mcg/kg of ASA was not self-administered until the 12th day of the drug period. Two out of three monkeys initiated responding for the combination during the drug period. The number of self-administered infusions did not exceed 50 per day. A third monkey did not intiate self-administration during the 14 day drug period. Both monkeys which engendered self-administration died on the 14th day of the experiment as a result of general intoxication. These experiments suggest that even toxic doses of ASA will not prevent monkeys from self-administration when offered together with a positive reinforcing drug such as codeine under a schedule of continuous self-administration

IV self-administration Acetylsalicylic acid (ASA) Combinations of ASA plus codeine

IN previous investigations [3,4] reinforcing properties of acetylsalicyclic acid (ASA) and combinations of the compound with codeine were studied. In those experiments reinforcing properties of ASA were assessed using substitution techniques in codeine experienced rhesus monkeys as well as in naive animals with access to the drug unlimited in time and amount.

Combinations of ASA with codeine, so far, have been studied in substitution experiments with codeine experienced animals only. These combinations engendered positive reinforcing properties, the number of infusions and the drug intake of the combinations being lower than that of the corresponding doses of codeine alone.

The purpose of the experiments described in this report was to assess whether self-administration of codeine/ASA-combinations found in cross self-administration experiments with limited access to the drugs was also evident in continuous self-administration experiments with unlimited access to the drugs.

METHOD

Animals

The animals were 12 rhesus monkeys (Macaca mulatta) weighing between 2.3 and 4.0 kg. Under sodium pentobarbital anaesthesia (30 mg/kg IV), the monkeys were surgically prepared with chronic silicone rubber catheters (Vivosil: outside diameter 2.2 mm, inside diameter 1.0 mm) which were passed through the internal jugular vein to the level of the right atrium.

Apparatus

The monkeys were fitted with metal harnesses for restraint. Each monkey was housed in an individual cubicle (76 cm wide, 91 cm high, 66 cm deep) equipped with a jointed metal restraining arm attached to the harness which allowed monkeys almost complete freedom in the cubicle. The front of the cubicle was open for observation and maintenance of the monkey.

The surgically implanted catheter led subcutaneously to the back of the monkey where it was brought out through a stab wound in the skin and passed through the restraining arm to an infusion pump (Cole Palmer Masterflex) mounted behind the cubicle. A response lever (Model 1380, Lehigh Valley Electronics Inc., Fogelsville PA) and a white stimulus light (2.4 W) were mounted on the rear wall of the cubicle. Each lever pressing response of more than 50 g

mass activated the automatic infusion pump which then infused 0.2 ml/kg of solution. Infusion time was regulated individually according to the weight of the animals (approximately 10 sec). One saline infusion was delivered automatically every four hours to prevent blood from clotting in the catheter. Details of catheterization procedure and the apparatus have been reported by Yanagita *et al.* [5] and Deneau *et al.* [1].

Procedure

After catheterization the monkeys were placed in individual cubicles where they lived for the duration of the experiment with food and water freely available. In order to prevent tuberculosis monkeys received 10 mg/kg of isoniazid in sweets daily.

Infusions were made available 24 hr a day under an one response fixed ratio (FR 1) schedule of drug infusion (continuous IV self-administration). At the beginning of the experiment the rate of self-administration of saline was determined for one week. Thereafter saline was replaced by ASA, codeine and ASA/codeine-combinations for a maximum of 14 days.

Four groups of three monkeys were presented with 50 mcg/kg/infusion of codeine, 2500 mcg/kg/infusion of ASA, 50 mcg/kg/infusion of codeine plus 2500 mcg/kg/infusion of ASA and 50 mcg/kg/infusion of codeine plus 10,000 mcg/kg/infusion of ASA.

The number of infusions per day and gross behavior were observed throughout the experiment.

Drugs

Codeine-phosphate; ASA, as lysine salt of acetylsalicylic acid. The water soluble ASA preparation contained ASA and lysine in equimolar amounts. In an aqueous solution, the lysine salt of ASA remains stable for several hours without hydrolysis into salicylic acid (the half life of this ASA preparation is about 40 hr in aqueous solution (pH 6.3); Pütter, personal communication).

In previous experiments it has been shown that single injections of the lysine salt of ASA were tolerated by monkeys in doses up to 350 mg/kg IV without behavioral signs of intoxication [3]. The influence of the lysine component of the preparation on self-administration behavior has been investigated in naive as well as in codeine trained monkeys. In three naive monkeys lysine (2.5 and 10 mg/kg/infusion), each dose offered over a period of two weeks, like saline did not engender self-administration behavior [3].

RESULTS

After presentation with 50 mcg/kg/infusion of codeine all three monkeys (Monkey 5.6; Monkey 15.0 and Monkey 14.0) initiated self-administration behavior (Fig. 1A). Monkey 5.6 self-administered more than 1000 infusions per day after 14 days exposure to the drug. The other two animals (Monkey 15.0 and Monkey 14.0) self-administered about 700 and 500 infusions per day respectively at the end of the experiment (Fig. 1B). The maximal daily codeine intake was 72 mg/kg (Monkey 5.6). All three animals showed no signs of intoxication.

After presentation with 2500 mcg/kg/infusion of ASA three other animals (Monkey 5.5; Monkey 11.6 and Monkey 16.0) did not initiate self-administration (not more

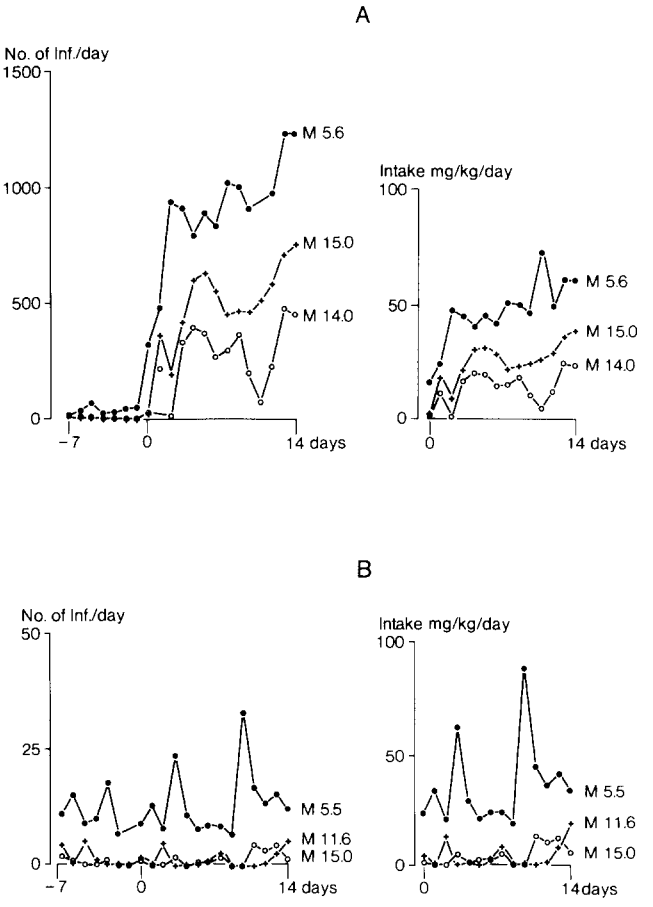

FIG. 1. A, left: Number of infusions of 50 mcg/kg of codeine of Monkeys 5.6, 15.0 and 14.0 over a period of 14 days; right: Daily codeine intake (mg/kg) in the same monkeys. B, left: Number of infusions of 2500 mcg/kg of ASA over a period of 14 days of Monkeys 5.5, 11.6 and 15.0; right: Daily ASA intake (mg/kg) of the same monkeys.

than 34 infusions as a maximum) throughout the 14 days of the experiment (Fig. 1A).

Replacement of saline by a combination of 50 mcg/kg/infusion codeine and 2500 mcg/kg/infusion of ASA did not result in self-administration during the first 9 days of drug exposure (Fig. 2A). From the 10th day on, all three monkeys (Monkey 11.6; Monkey 11.7 and Monkey 5.5) initiated self-administration, although the number of infusions was much lower than with codeine alone (not higher than 200 infusions per day) (Fig. 2A). Beginning with the second to the third day after initiation of responding, i.e. the 10th to the 12th day of drug exposure all three monkeys showed signs of central intoxication. These symptoms were characterized by ataxia, increased periods of sleep and impairment of the righting reflex.

Despite the central intoxication animals continued to respond for infusions until they died on the 12th, 13th or 14th day of the experiment respectively (Fig. 2A).

When ASA was given in this combination the maximal ASA intake varied from 490–580 mg/kg per day.

Postmortem investigations did not reveal histopathological changes in the heart, the liver and the kidneys.

Monkey 2.6 self-administered a combination of 50 mcg/kg of codeine plus 10,000 mcg/kg of ASA from the

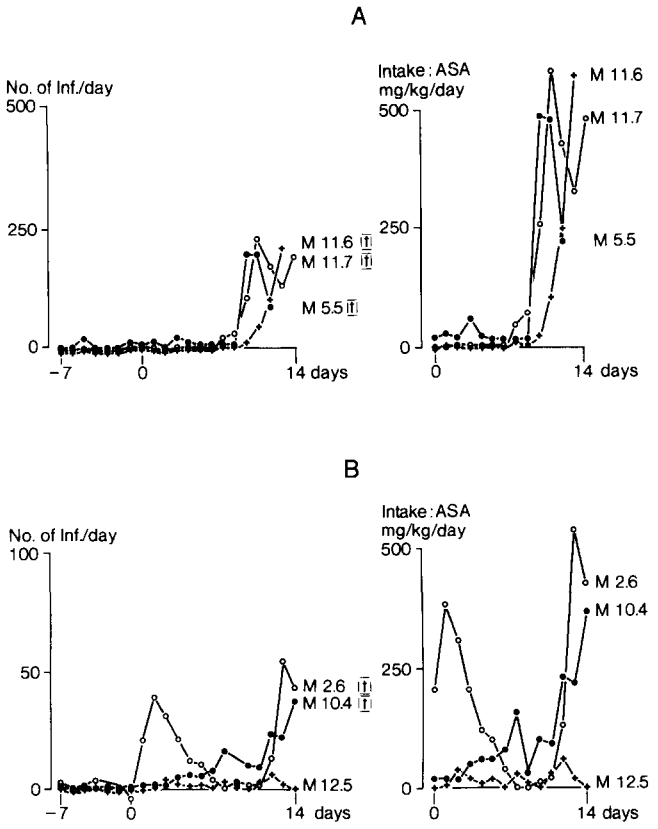

FIG. 2. A, left: Number of infusions of a combination of 50 mcg/kg of codeine plus 2500 mcg/kg/infusion of ASA of Monkeys 11.6, 11.7 and 5.5 (+ = death) over a period of 14 days; right: Daily ASA intake (mg/kg) of the same monkeys. B, left: Number of infusions of a combination of 50 mcg/kg of codeine plus 10,000 mcg/kg/infusion of ASA over a period of 14 days of Monkeys 2.6, 10.4 and 12.5 (+ = death); right: Daily ASA intake (mg/kg) of the same monkeys.

first to the seventh day of the drug period and then again from the 10th to the 14th day on which the animal died (Fig. 2B). Monkey 10.4 began self-administration on the 10th day and died also on the 14th day of the drug period. Monkey 12.5 did not self-administer ASA/codeine combinations (50 mcg/kg/infusion of codeine plus 10,000 mcg/kg/infusion of ASA). This animal survived without signs of intoxication whereas the other two monkeys showed symptoms identical with those described in the previous experiment with the codeine/ASA combination (50 to 2500 mcg/kg/infusion).

The maximal daily ASA intake of Monkey 2.6 and Monkey 10.4 was 570 mg/kg and 370 mg/kg respectively.

DISCUSSION

These experiments have confirmed the results achieved in substitution experiments in codeine experienced monkeys [3,4] indicating that the addition of ASA (lysine salt of acetylsalicylic acid) decreases rate of responding for codeine and total codeine intake in the rhesus monkey. It is, however, interesting, that under the schedule of continuous access rhesus monkeys will self-administer toxic and even lethal doses of ASA in combination with codeine.

As has already been demonstrated [3,4] intravenous injections of ASA alone do not serve as a positive reinforcer in the rhesus monkey. Experiments in which rhesus monkeys had to terminate infusions of ASA (0.5 and 1.0 mg/kg/infusion) or stimuli associated with such infusions failed to demonstrate negative reinforcing properties (Hoffmeister, in preparation; methodology see [2]) although the total drug intake per day exceeded 200 mg/kg of ASA IV. Thus, ASA seems to be devoid of positive and negative reinforcing properties.

Although these latter results are in correspondence with the finding that even toxic doses of ASA do not completely prevent self-administration of codeine when offered in combination, the cause for the decrease in self-administration of codeine/ASA combinations in drug naive and codeine experienced animals remains an open question.

In an attempt to assess the relative analgesic potencies of ASA, codeine and ASA plus codeine in rhesus monkeys using a titration avoidance procedure ASA alone (administered IV) exhibited no analgesic activity in doses up to 400 mg/kg (single injection). In this procedure animals pressed a lever in order to lower the strength of a noxious electrical stimulation of their heads. Five mg/kg of codeine (IV) alone increased the threshold for the initiation of lever pressing which in turn resulted in an increase in the voltage of the noxious electrical stimulus by 296% ($\bar{x}$ of 6 animals). A combination of 250 mg/kg of ASA with 5 mg/kg of codeine increased the threshold for titration avoidance responding by 752% ($\bar{x}$ of 6 animals). This difference was highly significant (Hoffmeister, unpublished results). Moreover, the duration of this increase in tolerance of the noxious stimulus was about 1.5 times longer with the codeine/ASA combination than the duration of the corresponding effect of codeine alone. These results indicate that codeine/ASA combinations in the rhesus monkey might have stronger analgesic effects with a longer duration than the respective doses of codeine alone.

Since the analgesic potency of opiates is to a certain extent correlated with the potency of their reinforcing properties one may speculate that the lower drug intake of codeine/ASA combinations in self-administration experiments can be explained by the possibility that also the positive reinforcing effect of each single codeine/ASA combination is stronger and longer lasting than the positive reinforcing effect of the respective dose of codeine alone. This assumption could in part explain the lower rate of self-administration of codeine/ASA combinations as compared to self-administration of codeine alone.

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