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Meperidine's Effects Under Shock Titration and Shock Discrimination Procedures[1]

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DYKSTRA, L. A. *Meperidine's effects under shock titration and shock discrimination procedures*. PHARMAC. BIOCHEM. BEHAV. 12(3) 403–407, 1980.—Meperidine's effects were examined under a schedule of shock titration and under a shock intensity discrimination in which squirrel monkeys discriminated between the presence and absence of a low intensity shock. Meperidine did not increase the intensity at which monkeys maintained the shock in the shock titration procedure, nor did meperidine alter the percentage of correct responses under the shock intensity discrimination although meperidine did increase the time to respond in the presence and absence of shock. When meperidine was combined with a dose of SKF-525A, which did not alter responding when given alone, the intensity at which monkeys maintained the shock under the shock titration procedure was increased. Moreover, the percentage of correct responses in the presence of shock under the shock titration procedure was decreased by the combination of meperidine and SKF-525A.

Meperidine Morphine SKF-525A Titration Discrimination Electric shock Squirrel monkeys

MEPERIDINE, a phenylpiperidine-derived narcotic, and morphine are both effective analgesics in man; however, these two drugs differ from each other in a number of ways including: (1) the extent to which each drug is antagonized by narcotic antagonists [10, 14, 16, 19]; (2) the occurrence of tolerance to the effects of each drug [14]; and (3) the fact that high doses of meperidine produce convulsions and other signs of central nervous system stimulation whereas high doses of morphine produce sedation and respiratory depression [12].

The purpose of the present study was to examine further differences between meperidine and morphine in two situations in which responding was determined by electric shock. In one situation squirrel monkeys responded under a discrete trial schedule of shock titration. Morphine and a number of other narcotic analgesics have been shown to increase the intensity at which shock is maintained in this procedure [6]. In the other situation squirrel monkeys discriminated between the presence and absence of low intensity electric shock. Morphine, methadone, pentazocine, cyclazocine and nalorphine have been shown to decrease discrimination of electric shock in this procedure [5,7].

Meperidine's effects were also examined in the presence of SKF-525A, an inhibitor of drug metabolism. There is evidence that large amounts of meperidine are metabolized to normeperidine, especially in the squirrel monkey [20]. In other species, SKF-525A inhibits the metabolism of meperidine to normeperidine [1], potentiates the analgesic effects of meperidine [3], and potentiates the rate-decreasing effects of meperidine [13].

EXPERIMENT 1

METHOD

Animals

Four adult male squirrel monkeys *(Saimiri sciureus)* were housed individually and maintained at free-feeding weights. All monkeys had continuous access to water and were given 12 Purina Monkey Chow biscuits and a vitamin C tablet every day. In addition, their diet was supplemented with fresh fruit.

Apparatus

A restraining chair similar to the one described by Hake and Azrin [11] was used. Each monkey was restrained in the seated position by a waist lock, and its tail was held motionless by a small stock. Electric current was delivered by two hinged brass plates which rested lightly on a shaved portion of the tail. The tail was massaged with noncorrosive electrode paste (EKG Sol) to ensure a low resistance electrical contact. The electric shock was 110 V AC, 60 Hz, delivered through a series resistance of about 180 kΩ. The shock intensity was adjusted through an add-subtract stepper (LVE-SS903/242-50) and a series of potentiometers.

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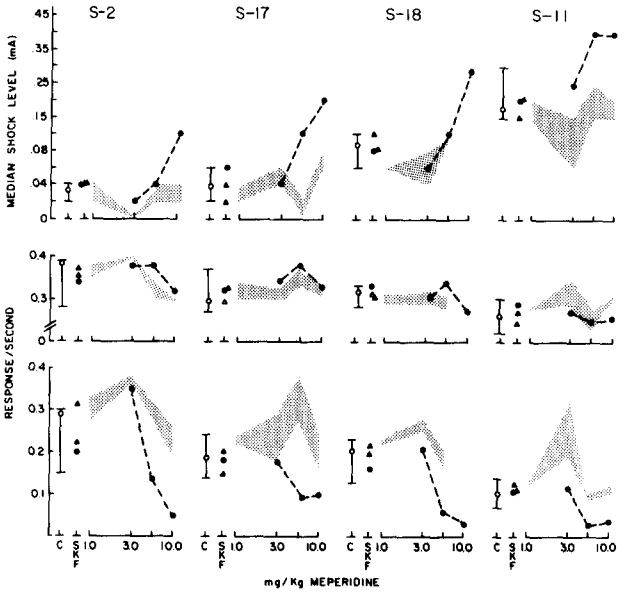

FIG. 1. Effects in four monkeys of meperidine alone and in combination with 50.0 mg/kg SKF-525A on median shock levels and on rates of responding in the presence of shock and in the absence of shock (i.e., during time out) under a shock titration schedule. Abscissae: dose of meperidine in mg/kg, log scale. Ordinates: top graphs, median shock level in mA; middle and bottom graphs, rate of responding in response/second. The brackets at C represent the range of control values and the open circles represent vehicle control days. Points at SKF show the effects of 25 (△), 50 (●), and 100 (▲) mg/kg SKF-525A alone. The shaded area is the range of values for two determinations of the meperidine dose-response curve. ● - - - ● is the dose-response curve for meperidine in combination with 50.0 mg/kg SKF-525A.

A response lever (BRS/LVE, model 121-05) was mounted on the right side of the front panel facing the monkey. When the lever was pressed with a minimal force of 30 g, a response was recorded and produced an audible click. The entire chair unit was enclosed in a ventilated sound-attenuating chamber. During the testing session, the interior of the chamber was illuminated by a 25-W bulb. Programming and recording equipment were located in an adjacent room. Continuous masking noise was present inside the experimental chamber.

Behavioral Procedure

A modification of the shock-titration procedure originally described by Weiss and Laties [24] and subsequently modified by Markowitz *et al.* [18] was employed. The shock increased from 0 to 2.0 mA in 30 steps (0, 0.02, 0.04, 0.06, 0.08, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.70, 0.80, 0.90, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 mA). During an experimental session, monkeys received continuous shock during 15 sec trial periods. If the monkey did not respond during the shock period, the shock remained on for the duration of the shock period, and increased by one increment on the next 15 sec trial period without an intervening time out period. If five responses were made during the shock period, the shock was immediately terminated for 15 sec during which the chamber was dark (time out). After the 15 sec time out period, the shock resumed at the next lower intensity.

Pharmacological Procedure

Doses of meperidine hydrochloride and β-dimethylaminoethyl-2,2-diphenylpropylacetate hydrochloride (SKF-525A) were calculated as the salt and dissolved in deionized water. Water was used for vehicle injections. Diazepam, which was administered only when convulsions occurred, was used as the free base and dissolved in the commercially available diazepam vehicle (40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers and 1.5% benzyl alcohol as preservatives).

Dose-response curves were first determined for meperidine alone, then for meperidine in the presence of SKF-525A and then redetermined for meperidine alone. Doses of meperidine were given in ascending order in half the monkeys and in descending order in the other half. Injections of meperidine were made into the leg muscle in a volume of 0.5 ml/kg BW; SKF-525A was given in a volume of 1.0 ml/kg BW. When SKF-525A and meperidine were given in combination, SKF-525A was injected in one leg 30 min before the experimental session and meperidine was injected in the other leg 10 min before the session. After each drug administration, monkeys were returned to their home cages. Injections generally were given every Tuesday and Friday. The data from Thursdays were used as non-injection control days. If the monkey ceased responding after drug injection, the sessions were terminated after 12.5 min, and higher doses of drug were not tested subsequently. If the monkey convulsed, the experimental sessions were terminated, and diazepam (1.7 mg/kg, IM) was administered. Previous work indicates that meperidine-induced convulsions are not blocked with 3.0 mg/kg naloxone, but they are blocked by 1.7 mg/kg diazepam [8].

Data Analysis

Rates of responding in the presence of shock were measured separately from rates of responding in the absence of shock. The number of times the five response requirement (FR 5) was completed was recorded as a function of the shock intensity at which the response requirement was completed. Median shock levels (the shock intensity below which the shock was kept 50% of the time) were derived from these data.

RESULTS

Figure 1 shows median shock levels and rates of responding in the presence and absence of shock (i.e., during time out) following meperidine alone and in combination with SKF-525A. Individual monkeys maintained the shock at a fairly constant level throughout the experimental session, although differences in the intensity at which the shock was maintained occurred between monkeys. Although median shock levels differed between monkeys (ranging from 0.02–0.30 mA), rates of responding during shock were similar between monkeys (ranging from 0.22–0.39 response/sec). Rates of responding during time out periods were generally lower and more variable than rates of responding during shock periods (ranging from 0.07 to 0.30 response/sec).

Meperidine alone, up to 10.0 mg/kg which produced convulsions in one monkey (S-18), either had no effect on median shock level or decreased it slightly. Meperidine consistently increased rates of responding in the absence of shock. Rates of responding in the presence of shock were increased slightly in selected monkeys.

When meperidine was combined with a dose of SKF-

525A (50.0 mg/kg) which had no effect when given alone, median shock levels increased and rates of responding in the absence of shock decreased. Rates of responding in the presence of shock were not altered by the combination of meperidine and SKF-525A.

EXPERIMENT 2

METHOD

Animals

Four adult male squirrel monkeys *(Saimiri sciureus)* were housed individually with continuous access to water. All monkeys were given sufficient Purina Monkey Chow biscuits to maintain them at 85% of their free-feeding body weights. In addition, their diet was supplemented with fresh fruit and a vitamin C tablet every day. All monkeys had been trained previously under a shock intensity discrimination and had received injections of several drugs [5,7].

Apparatus

Experiments were conducted with monkeys placed in small primate cockpits (BRS/LVE 142-11), enclosed in ventilated sound-attenuating cubicles. Each monkey was restrained in the seated position by a waist lock, and its tail was held motionless by a small stock. Electric current was delivered to the tail by two hinged brass bars which rested lightly on a shaved portion of the tail. The tail was massaged with a noncorrosive electrode paste (EKG Sol) to ensure low resistance electrical contact between bars and the tail. The electric shock (80 msec, 110 V AC, 60 Hz) was delivered through a series resistance of about 200 kΩ at a rate of ten pulses per second. The shock intensity was adjusted for each monkey by adding further resistance through a potentiometer.

Two response levers (BRS/LVE 121-05) were mounted 9 cm apart on the front panel of each chamber facing the monkey. When either lever was pressed with 25–30 g of force, a response was recorded and produced an audible click. Three recessed circular light panels were mounted 8.5 cm above the levers. Each chamber also contained a houselight, a 2.5 k Hz Sonalert, and a pellet dispenser which dispensed 190 mg Noyes banana pellets. Programming and recording equipment were located in an adjacent room. Continuous white masking noise was present inside the experimental chambers.

Behavioral Procedure

At the beginning of each session, the chamber was illuminated by the houselight. Stimulus periods were preceded by a 5-sec period during which responses reset a 5-sec timer. After 5 sec elapsed without a response, the lights above the levers were illuminated and shock was either presented or not (stimulus period). When shock was presented, it continued to pulse until the monkey responded on one of the two levers. A response on the right lever was designated as correct, and a response on the left lever was designated as incorrect in the presence of shock. In the absence of shock, a response on the left lever was designated as correct, and a response on the right lever was incorrect. Incorrect responses were followed by a 20 sec period during which the chamber was dark (time out). Every correct response was followed by a 30 msec, 2.5 kHz tone and on approximately 10% of the correct trials, by a 190 mg banana pellet. Delivery of the tone or food pellet was followed once again by the 5-sec houselight-only period preceding the onset of the lights over the levers. Daily sessions consisted of 300 stimulus periods, half of which were associated with presence of shock and half of which were associated with absence of shock. A quasi-random sequence was used to determine whether shock was present or absent during each stimulus period.

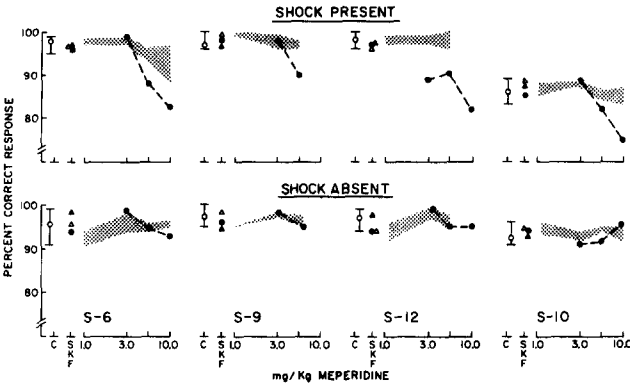

FIG. 2. Effects in four monkeys of meperidine alone and in combination with 50.0 mg/kg SKF-525A on the percentage of correct responses in the presence and absence of shock. Abscissae: dose of meperidine in mg/kg, log scale. Ordinates: top graphs, percentage of correct responses in the presence of shock; bottom graphs, percentage of correct responses in the absence of shock. The brackets at C represent the range of control values and the open circles represent vehicle control days. Points at SKF show the effect of 25.0 (△), 50.0 (●), and 100 (▲) mg/kg SKF-525A alone. The shaded area is the range of values for two determinations of the meperidine dose-response curve. ● - - - ● is the dose-response curve for meperidine in combination with 50.0 mg/kg SKF-525A.

Responses on both levers were recorded during each stimulus period, and the percentage of responses which were correct was obtained from these data. Additionally, response times were recorded from the onset of the stimulus period until a response occurred. Response times were analyzed separately in the presence and absence of shock.

In a previous experiment [5], the monkeys were trained to discriminate between the presence and absence of a shock of 0.35 mA and then to discriminate between the presence and absence of a shock intensity determined to be close to their psychophysical threshold by the method of limits. In three monkeys (S-6, S-9, S-12) this value was 0.05 mA; in Monkey S-10, it was 0.15 mA. In this experiment, Monkeys S-6, S-9 and S-12 discriminated between the presence and absence of 0.05 mA and Monkey S-10 discriminated between the presence and absence of 0.15 mA.

Pharmacological Procedure

Same as in Experiment 1.

Data Analysis

Drug effects are expressed as absolute changes in the percentage of correct responses and response time.

RESULTS

Figure 2 shows the effects in four monkeys of meperidine alone and in combination with SKF-525A on the percentage

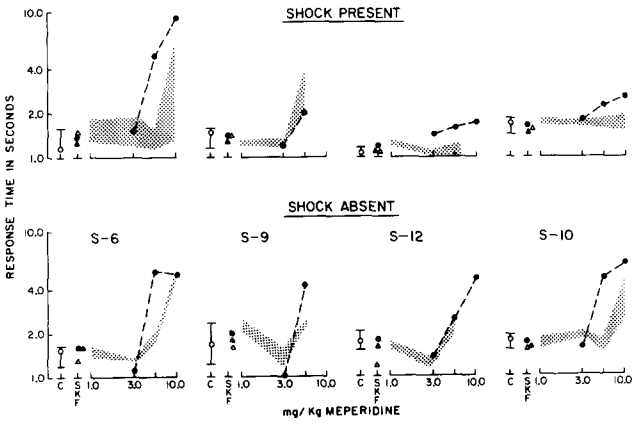

FIG. 3. Effects in four monkeys of meperidine alone and in combination with 50.0 mg/kg SKF-525A on response time in the presence and absence of shock. Abscissae: dose of meperidine in mg/kg, log scale. Ordinates: top graphs, response time in the presence of shock; bottom graphs, response time in the absence of shock. The brackets at C represent the range of control values and the open circles represent vehicle control days. Points at SKF show the effect of 25.0 (△), 50.0 (●) and 100 (▲) mg/kg SKF-525A alone. The shaded area is the range of values for two determinations of the meperidine dose-response curve. ● - - - ● is the dose-response curve for meperidine in combination with 50.0 mg/kg SKF-525A.

of correct responses in the absence or presence of shock. All monkeys were 90% correct or better at detecting the absence of shock. The percentage of correct responses in the presence of shock was also at least 90% correct in Monkeys S-6, S-9 and S-12 and slightly lower in S-10. Meperidine up to a dose of 10.0 mg/kg did not consistently alter the percentage of correct responses either in the presence or absence of shock. Higher doses of meperidine were not examined since 10.0 mg/kg produced convulsions in one monkey and completely eliminated responding in another. When meperidine was combined with a dose of SKF-525A which had no effect when administered alone, the percentage of correct responses in the presence of shock decreased in all monkeys in a dose-related manner. The percentage of correct responses in the absence of shock was not altered by the meperidine-SKF-525A combination.

Figure 3 shows the effects in four monkeys of meperidine alone and in combination with SKF-525A on response time in the absence or presence of shock. In general, meperidine increased response time both in the presence and absence of shock. Increases in response time were even greater when meperidine was combined with SKF-525A.

DISCUSSION

The effects of meperidine alone under a shock discrimination and a shock titration schedule are markedly different from the effects of morphine and other narcotic analgesics. A variety of narcotic analgesics increase the intensity at which monkeys and rats maintain a shock under shock titration procedures [9, 17, 22, 23], including a procedure identical to the one employed in the present experiment [6]. In the present experiment, meperidine alone did not increase the intensity at which squirrel monkeys maintained shock. This is consistent with previous findings that neither meperidine nor anileridine (another phenylpiperidine-derived narcotic which is metabolized to normeperidine [15]) increase the intensity at which squirrel monkeys maintain a shock under a shock titration procedure [8]. Nevertheless, when meperidine was combined with SKF-525A, which inhibits the rate of metabolism of meperidine to normeperidine [1], meperidine increased the intensity at which squirrel monkeys maintained a shock about three fold. Such increases are comparable to those previously reported for morphine in squirrel monkeys responding under a shock titration procedure identical to the one examined here in which morphine increased median shock levels three to four fold [6].

In addition, meperidine has effects on discrimination of a low intensity shock which are different from those of other narcotic analgesics. In previous studies [5,7], morphine, methadone, pentazocine, cyclazocine and nalorphine decreased detection of the presence of a low intensity shock (0.05–0.15 mA). For example, morphine decreased the percentage of correct shock detections from a control level of 90% correct to between 60 and 80% correct. In the present experiment, meperidine only decreased detection of a low intensity shock when combined with SKF-525A and decreases were generally less than those observed following morphine (i.e., from control levels of 90% correct to 75–80% correct).

The fact that meperidine alone did not alter responding under either a shock titration or a shock discrimination procedure may be due to the fact that large amounts of meperidine are metabolized to the convulsant normeperidine which is devoid of narcotic-like effects [2, 4, 13, 21]. Moreover, there is evidence that the squirrel monkey is more capable of forming the convulsant normeperidine than are other species [20]. Two of the eight squirrel monkeys in the present experiment convulsed at 10.0 mg/kg meperidine. Convulsions also occurred in the one monkey that received 17.0 mg/kg meperidine. These convulsions could not be antagonized by naloxone. This is consistent with other reports that the effects of high doses of meperidine are not blocked by narcotic antagonists [10, 13, 14]. In addition, convulsions did not occur at these doses when conversion of meperidine to normeperidine was inhibited with SKF-525A. Meperidine also produces convulsions in rhesus monkeys; however, when these monkeys are pretreated with SKF-525A, the meperidine-induced convulsions are replaced by sedation [4].

In conclusion, meperidine's effects in the squirrel monkey are qualitatively different from those of morphine and other narcotic analgesics in at least two situations. In a shock titration procedure, morphine increases median shock level and decreases rates of responding in the absence of shock, whereas meperidine does not. In a shock discrimination procedure, morphine decreases detection of a low intensity shock, whereas meperidine does not. Nevertheless, when the metabolism of meperidine to normeperidine is inhibited by SKF-525A, meperidine has effects similar to those of morphine.

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