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Effects of Concomitant Pentazocine and Tripelennamine on Brain-Stimulation Reward[1]

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UNTERWALD, E. M. AND C. KORNETSKY. *Effects of concomitant pentazocine and tripelennamine on brain-stimulation reward.* PHARMACOL BIOCHEM BEHAV **21**(6) 961–964, 1984.—Reinforcing thresholds for self-stimulation behavior to the medial forebrain bundle were determined in rats by means of a rate-free psychophysical method. The acute administration of either pentazocine or tripelennamine caused a small but significant lowering of the reward threshold. Combined administration of an ineffective dose of tripelennamine with various doses of pentazocine resulted in a potentiation of this lowering effect. These results suggest that the widespread abuse of the combination of pentazocine and tripelennamine may be due to a pharmacologic potentiation rather than just a summation of their two effects.

Brain-stimulation reward Pentazocine Tripelennamine Threshold determination

IN recent years, the abuse of pentazocine combined with tripelennamine has become widespread. Substitution of this drug combination for heroin in periods of low, or poor quality, heroin availability has been documented by numerous urban centers [5,8]. This combination, commonly referred to as "T's and Blues," reportedly gives the user a more heroin-like effect than is experienced with pentazocine alone [7]. The mechanism by which tripelennamine, an antihistaminic/anticholinergic, enhances the euphoric effects of pentazocine, a mixed agonist/antagonist opioid, is unclear.

It has previously been demonstrated that a variety of abused substances, including morphine, cocaine, amphetamine, and phencyclidine, lower the threshold for rewarding brain stimulation suggesting that this is a useful model for studying the hedonic effects and abuse liability of many drugs [4]. We have recently reported that tripelennamine alone significantly lowered the threshold for rewarding intracranial stimulation in this model [10]. Although facilitation of the reward system was observed with tripelennamine, the magnitude of this effect was substantially less than what has been observed in previous studies with more highly abused drugs such as morphine, cocaine, or amphetamine. This suggests that tripelennamine is only weakly euphorigenic compared to other drugs of abuse. The present study investigates the effect of the combined administration of pentazocine and tripelennamine on reward threshold and compares this effect with that observed when each drug is given alone.

METHOD

Five male albino rats (CDF—Charles River Laboratory) weighing approximately 300 g, were anesthetized with Equi-Thesin® (0.9 ml) and stereotaxically implanted bilaterally with bipolar stainless steel electrodes (0.0127 cm in diameter and insulated except at the tips) aimed at the lateral hypothalamic region of the medial forebrain bundle (MFB-LH coordinates—4.0 mm posterior to the bregma, ±1.4 mm from the midline suture, and 8.5 mm ventral to the skull surface). The electrodes were placed through small burr holes in the skull and attached permanently to the surface with an acrylic platform. After surgery, animals received 60,000 units of penicillin (Bicillin®) IM and were given at least one week for post-operative recovery before behavioral testing was begun. Animals were maintained on a 12 hour light/dark cycle, housed in standard steel cages and had ad lib access to food and water.

Animals were trained and tested on a rate-independent threshold procedure [2] in a Plexiglas chamber (20×20 cm). A cylindrical manipulandum (7.5×15 cm) was located within one wall of the test chamber. Four equally spaced cams on one endplate of the manipulandum operated a microswitch which resulted in immediate delivery of a stimulation when the cylinder was rotated one-quarter of a turn. A constant current stimulator (Sunrise Systems, Pembroke, MA) was used to deliver the biphasic symmetrical pulses. Each stimulus consisted of a 500 msec train with a pulse width of 0.2 msec and a delay of 0.2 msec between the positive and negative pulses at a frequency of 160 Hz.

Thresholds were determined by a procedure involving the use of discrete trials systematically presented over a range of stimulus intensities. A trial began with the delivery of a noncontingent stimulus. A response of one-quarter wheel turn within 7.5 sec of this stimulus resulted in the delivery of a contingent stimulus, identical in all parameters to the noncontingent stimulus, and terminated the trial. Failure to re-

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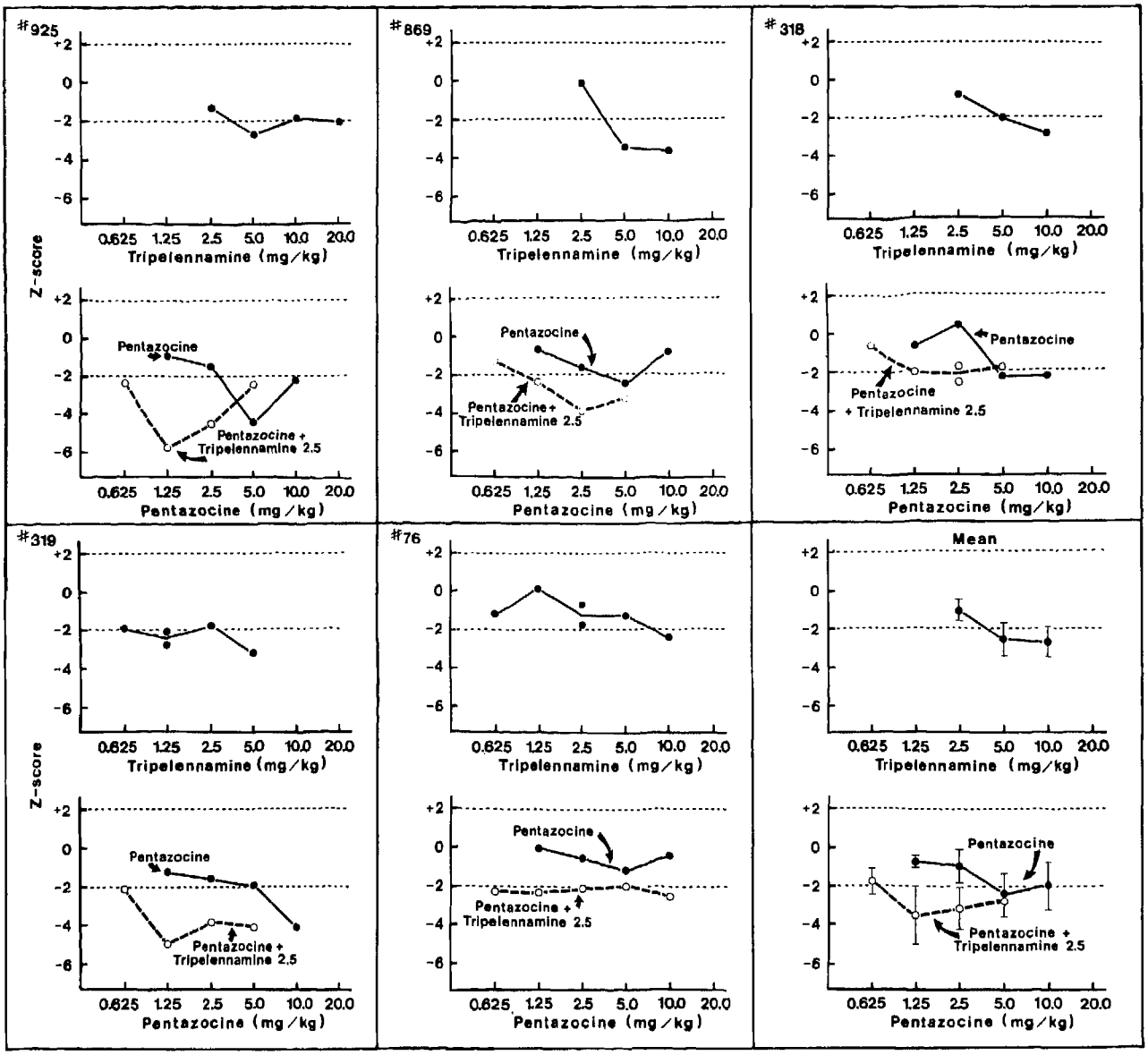

FIG. 1. Standard score (Z-score) changes in reward threshold value from pre- to post-drug for each of five animals. The upper graph for each animal shows the effects of tripelennamine alone. The lower graph displays the effect of pentazocine alone and the combination of various doses of pentazocine with 2.5 mg/kg tripelennamine. A Z-score of ±2 indicates the 95% confidence levels. Mean Z-scores for the five animals are also shown in the lower right corner.

spond had no scheduled consequences and the trial was terminated after 7.5 sec. The interval between trials varied around an average of 15 sec and responses during the intertrial interval (error responses) resulted in a 15 sec delay before the start of the next trial.

Stimulus intensities were varied using a modification of the classical method of limits. Stimuli were presented in an alternating descending and ascending series with a step size of 3, 5 or 10 μA (depending on the sensitivity of the individual animal) with 5 trials at each intensity level before the next lower or higher intensity was presented. Subjects completed 4 series (i.e., descending, ascending, descending, and ascending) prior to injection and then 8 series post-injection, with the entire pre-, post-session lasting 2.5 to 3 hours. All experimental data was collected and stored by an on-line microcomputer. Each series' threshold value was defined as the midpoint in microamperes between the level at which the animal made 3 or more responses out of 5 stimulus presentations (a plus score) and the level where less than 3 responses (a minus score) was made.

Animals required approximately 6 one hour training sessions to learn the task and approximately 4 additional sessions for the establishment of a stable threshold level whereupon intraperitoneal vehicle injections were begun. Animals were tested with vehicle injections for 5 days before drug administration was initiated. Also, vehicle days were always interspersed between each day of drug treatment so that animals received drug only twice weekly.

Animals were injected intraperitoneally with either tripelennamine hydrochloride dissolved in isotonic saline,

pentazocine (Talwin®) injectable solution (30 mg/ml) diluted with isotonic saline, or vehicle control. All injections were in volumes of 1 ml/kg body weight and the post-injection testing session was begun 10 minutes after drug or vehicle administration. The sequence of doses was balanced between animals.

Threshold values were calculated for both the pre-injection and the post-injection sessions, with the difference between the two scores taken as the dependent measure. These difference scores were transformed to standard scores (Z-scores) based on the mean and standard deviation of the difference scores for all vehicle control days. A Z-score of ±2.0 (95% confidence level) was preselected as the level of significance.

Dose-effect curves were generated for both tripelennamine and pentazocine alone. A dose of tripelennamine which was ineffective in lowering the threshold for brain-stimulation reward was then co-administered with various doses of pentazocine. Once again, difference scores from pre- to post-injection of the combination were converted to Z-scores and were then compared to the Z-scores obtained from pentazocine alone.

RESULTS

The results obtained with each animal are shown in Fig. 1. The upper graph in each case displays the effect of 0.625 to 20.0 mg/kg tripelennamine alone on the threshold for rewarding brain stimulation. The lower graph displays the effect of 0.625 to 10.0 mg/kg pentazocine alone and the combination of these doses with 2.5 mg/kg tripelennamine. All animals showed a dose-dependent lowering of the reinforcing threshold following administration of tripelennamine. Four animals showed a lowering of threshold with pentazocine. A fifth animal (No. 76) showed a trend towards a lowering effect but never reached significance. When an ineffective dose of tripelennamine (2.5 mg/kg) was administered concomitantly with pentazocine, a greater lowering of the reward threshold was seen. The magnitude of this effect was often more than additive and always exceeded that observed with either drug alone at any dose.

DISCUSSION

Administered alone, both pentazocine and tripelennamine lowered the threshold for rewarding brain stimulation to the MFB-LH area. Although significant enhancement of the reward system was observed, the degree of this facilitation was substantially less than that observed in previous studies with highly abused substances such as morphine, cocaine, or amphetamine [4]. In contrast, when a small dose of tripelennamine which was ineffective alone in lowering the reward threshold was administered concomitantly with pentazocine, a significantly greater lowering effect was observed. The combination of pentazocine and tripelennamine in many instances produced a lowering of the threshold for rewarding intracranial stimulation equal in magnitude to that observed with morphine, cocaine, or amphetamine suggesting a marked synergistic increase in euphoria when these two drugs are co-administered.

The mechanism by which tripelennamine enhances the abuse liability of pentazocine is poorly understood. The pharmacologic interaction of these two drugs has been studied in other procedures. Enhancement of pentazocine's antinociceptive activity by tripelennamine has been demonstrated in mice using the hot plate method by Tagashira *et al.* [9]. They found that the antinociceptive effects of this combination, as well as those of tripelennamine alone, were completely inhibited by naloxone (0.1–1.0 mg/kg) indicating involvement of the opiate system. Utilizing a modification of the Haffner's tail clamp procedure, Hui *et al.* [3] showed that tripelennamine had weak analgesic activity in mice, but that this analgesia was only partially abolished by naloxone suggesting that opiate, as well as non-opiate, mechanisms are involved. They also demonstrated that tripelennamine potentiated the antinociceptive effects of nalbuphine, another mixed agonist/antagonist opioid.

The effects of the combination of pentazocine and tripelennamine on behavioral measures have also been studied. In rats trained to discriminate morphine from saline, Shannon and Su [7] showed that tripelennamine significantly enhanced the morphine-like discriminative stimulus effects of pentazocine. In rats trained to discriminate SKF 10,047 (the prototypic psychotomimetic narcotic derivative) from saline, tripelennamine markedly reduced the SKF 10,047-like discriminative stimulus effects of pentazocine. These results led the authors to speculate that tripelennamine might act by reducing the dysphoric psychotomimetic component of pentazocine which has been reported in humans at high doses. In addition, Shannon and Su [7] report that tripelennamine did not effect pentazocine's inhibition of the twitch-height of the electrically stimulated guinea pig ileum, nor did it modify the k_e for naloxone in antagonizing pentazocine, nor did it affect the inhibition of specific (^{3}H)-naloxone binding by pentazocine. Taken together, these results suggested that the potentiation of pentazocine by tripelennamine seen at the behavioral level is not due to molecular interactions at the morphine receptor.

Alternatively, tripelennamine's interaction with pentazocine may be mediated via a central histamine system. In rats, it has been shown that chronic treatment with morphine results in a significant decrease of histamine in the CNS [6] and that naloxone can reverse or block these effects of morphine on brain histamine [1]. Administration of L-histidine can enhance morphine tolerance and inhibit morphine physical dependence [12]. Similarly it has been demonstrated that H_1 and H_2 receptors in the brain are involved in the development of morphine tolerance and physical dependence in mice [13]. This pharmacologic relationship between narcotic addiction and central histamine may be related to the interaction of pentazocine and tripelennamine.

Another interaction of this combination was studied by Waller *et al.* [11]. They demonstrated that tripelennamine potentiated the lethal effects of pentazocine in mice in that tripelennamine (20–40 mg/kg) decreased the LD50 of pentazocine from 116 mg/kg to 8 mg/kg. No mechanism was speculated.

In conclusion, the results of this study demonstrate that both pentazocine and tripelennamine alone cause a significant, but modest, lowering of the threshold for rewarding brain stimulation to the MFB-LH area in the rat. Co-administration of a low dose of tripelennamine with pentazocine resulted in a potentiation of this lowering effect. The dose-response curve of pentazocine was shifted downward and to the left with concomitant tripelennamine administration, the former indicating an increase in euphoria and abuse liability and the latter indicating an increase in potency. These results suggest that although pentazocine and tripelennamine each have primary reinforcing properties, that their widespread abuse in combination may be due to a pharmacologic potentiation rather than just a summation of their two effects.

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