INFLUENCE OF PRETREATMENT WITH A MONOAMINE OXIDASE INHIBITOR (PHENELZINE) ON THE EFFECTS OF BUPRENORPHINE AND PETHIDINE IN THE CONSCIOUS RABBIT

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A severe toxic interaction occurs when patients, treated with monoamine oxidase (MAO) inhibitors, are given the narcotic analgesic pethidine [1—4]. The symptoms exhibited by these patients include cyanosis, profuse sweating and Cheyne-Stokes ventilation. Patients become semi-conscious, may pass into coma and have died [2].

Although there has not been any report of such an interaction between buprenorphine and MAO inhibitors, it is important that the possibility of such an interaction be investigated.

It is possible to demonstrate the MAO inhibitor—pethidine interaction in mice [5,6], rats [7] and rabbits [7,8]. The rabbit was chosen as the subject of this study as the interaction is particularly marked (especially on body temperature). In addition, arterial pressure and heart rate are readily monitored in the conscious rabbit.

Previous studies of this interaction have used a range of doses of phenelzine varying from 10 h pretreatment with 5 mg kg−1 [7] to 50 mg kg−1 at 42 and 18 h before administration of pethidine [8]. The dose of pethidine most commonly used is 5 mg kg−1. In the present study, preliminary investigations using a range of doses and pretreatment times with phenelzine showed that a strong interaction with pethidine 5 mg kg−1 i.v. occurred after pretreatment with phenelzine 20 mg kg−1 s.c., given 18–24 h previously. The doses of buprenorphine were chosen from analgesic data in the conscious rabbit, where 0.1 mg kg−1 i.v. was a threshold dose, the ED50 was 0.2 mg kg−1 and maximum analgesia was produced with 1.6 mg kg−1 i.v. [9]. As buprenorphine exhibits a “bell-shaped” dose–response curve, producing less effect with higher doses, a low dose (0.1 mg kg−1) and a high, but submaximal, analgesic dose (1.0 mg kg−1) were chosen.

SUMMARY

The existence of a severe toxic interaction (occasionally fatal) from the clinical use of pethidine and monoamine oxidase (MAO) inhibitors is well established. The present study evaluates the possibility of such an interaction existing for the opioid partial agonist buprenorphine. Conscious rabbits (n = 6 in each group) pretreated 18–24 h previously with physiological saline or the MAO inhibitor phenelzine 20 mg kg−1 s.c. were subsequently given physiological saline, pethidine 5 mg kg−1 i.v. or buprenorphine 0.1 or 1.0 mg kg−1 i.v. Whilst saline was without effect and phenelzine produced only a small increase in the rabbit temperature, the combination of phenelzine and pethidine produced a marked, prolonged hyperpyrexia (+4.4±0.19 °C; P < 0.001), hypertension (+33.9±3.1 mm Hg; P < 0.01) and agitation. Three rabbits died, at 35, 45 and 55 min after the pethidine-phenelzine combination. Buprenorphine was without significant effect on any parameter when given after phenelzine. In the model used buprenorphine, in contrast to pethidine, showed no interaction with the MAO inhibitor phenelzine.

MATERIALS AND METHODS

Male, New Zealand white rabbits in the weight range 1.8–2.75 kg were treated with either...
physiological saline 1 ml kg\(^{-1}\) s.c. or phenelzine 20 mg kg\(^{-1}\) s.c. 18–24 h before study. On the day of the investigation the rabbits were lightly anaesthetized with halothane to allow the placement of a rectal thermometer probe (Bailey Instruments, Type RET-1); the resulting body temperature was displayed on a digital temperature display (Bailey Instruments, Model BAT 8). Whilst the animal was anaesthetized, a 23-gauge Mediwing infusion set was inserted to an ear vein to allow administration of the test compounds. Similarly, a 23-gauge needle, connected to a Hewlett-Packard 1280C pressure transducer via a length of polypropylene tubing (pp 50), filled with heparinized saline 20 units ml\(^{-1}\), was inserted to an ear artery for the recording of arterial pressure via a Hewlett-Packard 8805C carrier amplifier. The recording of arterial pressure was used to calculate heart rate. The animals were allowed to recover from the anaesthesia before the start of the definitive investigation. Body temperature, arterial pressure and heart rate were monitored every 10 min for up to 30 min before the administration of test drugs, to ensure the stability of all variables. The animals then received pethidine 5 mg kg\(^{-1}\) i.v., buprenorphine 0.1 or 1.0 mg kg\(^{-1}\) i.v. or physiological saline 1 ml kg\(^{-1}\) i.v. Variables were monitored every 5 min for up to 60 min following the administration of the test compound.

**Drugs**

Buprenorphine (Reckitt and Colman); pethidine (Macfarlan-Smith); phenelzine SO\(_4\) (Sigma). Drugs were dissolved and diluted in 0.9% sodium chloride (Boots, Steriflex). The dose volume for all drugs was 1 ml kg\(^{-1}\).

**Data analysis**

The mean effect at each measurement was calculated and the standard error of the mean

![Graphs](image-url)
determined. Student's t tests were used to determine the level of statistical significance.

RESULTS

Body temperature

Saline. Rabbits pretreated 18–24 h previously with physiological saline 1 ml kg\(^{-1}\) s.c. or phenelzine 20 mg kg\(^{-1}\) s.c. showed no change in body temperature when subsequently given saline 1 ml kg\(^{-1}\) i.v. (fig. 1A). However, those rabbits pretreated with phenelzine had significantly higher pre-challenge temperatures (\(P < 0.02\)) than the saline-pretreated group.

Buprenorphine. Buprenorphine 0.1 mg kg\(^{-1}\) or 1.0 mg kg\(^{-1}\) i.v., when given to rabbits pretreated with either phenelzine or saline, was without effect on body temperature (fig. 1C, D). However, there was a significant difference in temperature between the phenelzine- and saline-pretreated groups (\(P < 0.05\) and \(P < 0.02\)), the phenelzine group having the higher temperatures. Buprenorphine did not cause any changes in the behaviour of the animals in either the saline- or phenelzine-treated animals.

Pethidine. Pethidine 5 mg kg\(^{-1}\) i.v. caused a large increase in body temperature (+4.4 ± 0.19 °C; \(P < 0.001\)) in those animals which had been pretreated with phenelzine. The increase in body temperature was rapid in onset and was statistically significant (\(P < 0.01\)) from 5 min after the administration of the pethidine, and continued to increase for the duration of the investigation (fig. 1B). The combination of pethidine and phenelzine produced gross changes in animal behaviour: the rabbits exhibited symptoms of hyperexcitement, tremor and increased motor restlessness, including nodding and jumping. Three rabbits died after the combination of phenelzine and pethidine (35, 45 and 55 min after the pethidine).
MAOI AND OPIATE INTERACTION

In saline-pretreated rabbits, pethidine did not produce an alteration in body temperature (fig. 1B), nor did the animals show any changes in behaviour. As with the other test groups, phenelzine-pretreated animals had significantly higher starting temperatures ($P < 0.01$) than the saline-pretreated group.

Arterial pressure and heart rate

Saline. When given to rabbits pretreated with either physiological saline or phenelzine, there were small non-significant decreases in mean arterial pressure (fig. 2A) and heart rate (fig. 3A).

Buprenorphine. In animals pretreated with saline, the lower dose of buprenorphine 0.1 mg kg$^{-1}$ i.v. was associated with a small, but not significant decrease ($-9.4\pm5.7$ mm Hg), in arterial pressure (fig. 2C). There was no change in heart rate (fig. 3C). The higher dose of buprenorphine (1.0 mg kg$^{-1}$ i.v.) was without effect on arterial pressure (fig. 2D); there was a small ($-26.7\pm12.0$ beat min$^{-1}$) although not-significant decrease in heart rate (fig. 3D).

Buprenorphine 0.1 and 1.0 mg kg$^{-1}$ i.v. given to rabbits 18–24 h after phenelzine pretreatment was without effect on arterial pressure (fig. 2C, D) and produced only small, and not-significant, changes in heart rate (fig. 3C, D).

Pethidine. In saline-pretreated rabbits the administration of pethidine 5 mg kg$^{-1}$ i.v. resulted in a small, but non-significant increase in arterial pressure. After pretreatment with phenelzine, pethidine produced an increase in mean arterial pressure (fig. 2B). The change in arterial pressure produced by pethidine seen in the phenelzine-pretreated group ($+33.9\pm3.1$ mm Hg) was significantly different ($P < 0.05$) from the change in arterial pressure produced in the saline-pretreated group ($+14.3\pm6.8$ mm Hg). However, the increase in arterial pressure with the pethidine-phenelzine combination was highly significant relative to both pre-pethidine controls.

![Heart rate and arterial pressure graphs](image_url)
and the saline control group \( P < 0.001 \). Whilst pethidine, in saline-pretreated animals, resulted in a significant \( P < 0.001 \) decrease in heart rate \((-102.5 \pm 12.0 \text{ beat min}^{-1})\), in phenelzine-treated animals it produced a progressive tachycardia (maximum change \(+42.5 \pm 21.7 \text{ beat min}^{-1}\) (fig. 3B).

**DISCUSSION**

It was clear from the present investigation that the interaction between pethidine and phenelzine is very severe, confirming the studies by Jounela [7] and Loveless and Maxwell [8]. The interaction was much more severe than the 1–1.5 °C increase that would result as a response to a bacterial pyrogen. Bacterial pyrogen responses were not evident in the present study, with no changes in temperature after i.v. administration in the saline group. The increase in temperature after the combination of phenelzine and pethidine was of rapid onset and developed throughout the whole period of observation. This was in contrast to the effects on arterial pressure, which peaked within 5 min of the injection of pethidine.

The observation that pethidine alone produced a small pressor response and marked bradycardia also confirmed the results of Jounela [7], who attributed these effects of pethidine to an indirect release of catecholamines. The lack of bradycardia after phenelzine pretreatment may be the result of further enhancement of catecholamine concentrations such that direct cardiac stimulation opposed the reflex bradycardia. It is not clear by what mechanism the pethidine–phenelzine interaction occurs, although it has been shown that inhibition of both A and B types of MAO are required for pethidine to produce the effect [10]. Although there are a number of publications implicating increased concentrations of 5-hydroxytryptamine (5-HT), the effect is not only related to 5-HT concentrations but may, in addition, be caused by increased concentrations of dopamine or noradrenaline, or both [11], which may account for the differing time courses of the changes in cardiovascular indices and in temperature. The effect of the MAO inhibitor agent is not simply the result of a reduction in metabolism, as complete inhibition of the liver microsomal enzymes which metabolize pethidine does not induce the toxic effects noted [10]. Whatever the cause of the pethidine–MAO inhibitor interaction, it is clear from the present studies that buprenorphine does not interact with the MAO inhibitor phenelzine. Morphine is similarly without toxic sequelae when administered in conjunction with a MAO inhibitor [7, 12–15]. Penn and Rogers [14] also showed that the opioid pentazocine did not produce a toxic interaction with the MAO inhibitor pargyline. In addition, there are no reports of clinical observations of a toxic interaction between MAO inhibitors and opioids other than pethidine. Thus, it would appear that MAO inhibitors have a very specific interaction with pethidine, and that a general interaction with opioids does not exist.

**REFERENCES**
