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Comparison of the effects of morphine, pethidine and pentazocine in rabbits pretreated with a monoamine oxidase inhibitor

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Summary

1. Rabbits were premedicated with pargyline and the changes in rectal temperature measured after the intravenous infusion of morphine, pentazocine and pethidine.

2. Pethidine produced pronounced rises in rectal temperature which were dose dependent. One out of the four rabbits given 1 mg/kg died in hyperthermia. Four out of the four rabbits given 5 mg/kg died in hyperthermia. Doses of 10 mg/kg of pethidine caused no significant change in the rectal temperature of rabbits not pretreated with pargyline.

3. Morphine and pentazocine in doses of 1 mg and 10 mg/kg did not significantly alter the rectal temperature of rabbits pretreated with pargyline except for one rabbit which developed a delayed hyperthermia following the injection of morphine 1 mg/kg.

Introduction

In patients undergoing long term treatment with monoamine oxidase (MAO) inhibitors, therapeutic doses of pethidine have caused severe toxic reactions characterized by symptoms which include motor restlessness, excitement and hyperthermia (Mitchell, 1955; Goldberg, 1964; Sjöqvist, 1965; Stockley, 1969). Pethidine appears to be the only potent analgesic implicated in this interaction. No adverse reactions have occurred when morphine has been administered to patients undergoing treatment with MAO inhibitors (Palmer, 1960; Shee, 1960). Investigations with mice, however, have shown that, in addition to pethidine, the toxic effects of other potent analgesics are increased by the prior administration of MAO inhibitors (Mustala & Jounela, 1966; Rogers & Thornton, 1969). Nevertheless, this increased toxicity only occurs following the acute administration of very large doses of the MAO inhibitor. It seemed of interest, therefore, to study the drug-drug interaction using an experimental model and drug treatment more closely related to the situation as it occurs in man.

Nymark & Nielsen (1963) and Loveless & Maxwell (1965) reported that pethidine causes excitation and hyperpyrexia in rabbits pretreated with an MAO inhibitor. This abnormal reaction to pethidine resembles that which occurs in man. Thus, the rabbit seemed a suitable model to use in this investigation. Pargyline has been chosen as the MAO inhibitor since it is currently used as an antihypertensive drug,

and Spector, Hirsch & Brodie (1963) have extensively investigated the effects of chronic pargyline treatment in the rabbit. Morphine, pethidine and pentazocine were chosen as representing different chemical classes of potent analgesic drugs.

Methods

The experiments were carried out on New Zealand White or Californian rabbits of either sex, weighing 1·5–2·5 kg. On 5 successive days the rabbits were injected with the MAO inhibitor (pargyline 25 mg/kg) by the subcutaneous route (Spector *et al.*, 1963). The injections were made between 9 and 10 a.m. On day 5 the rabbits were placed in stocks for the recording of the rectal temperature. Five hours after the last dose of pargyline the analgesic drug was slowly infused into a marginal ear vein. Control animals received 0·9% NaCl solution (saline). Rectal temperature was measured by a thermistor probe inserted 8–10 cm into the rectum. The temperature was recorded on an electric thermometer (Light Laboratories, Brighton).

Drugs

The drugs used were pargyline hydrochloride (Abbot Laboratories), morphine hydrochloride, pethidine hydrochloride and pentazocine hydrochloride (Winthrop Laboratories). All doses are expressed in terms of the salts which were dissolved in Sodium Chloride Injection B.P.

Results

Rabbits not pretreated

None of the analgesic drugs used caused a significant change in the body temperature of rabbits not pretreated with pargyline (Table 1). The most prominent symptoms produced by the higher doses were ataxia and respiratory depression. Saline injected into pargyline pretreated rabbits also did not cause any significant change in temperature.

Rabbits pretreated with pargyline

Pethidine

This was injected in three dose levels: 1, 2·5 and 5 mg/kg. There was an obvious dose-effect relationship since fatal hyperthermia was caused in one out of four

TABLE 1. *Effect of intravenous injections of pethidine, morphine and pentazocine on the rectal temperature of the rabbit not pretreated with pargyline*

Drug	Dose (mg/kg)	Number of animals	Mean rectal temperature (°C) Time from injection (min) −30	0	+30	+60	+120
Saline	—	3	39·6	39·7	39·6	39·5	39·6
Saline (pargyline pretreated)	—	4	40·2	40·0	40·0	40·1	40·3
Pethidine	1	2	39·7	39·7	39·8	39·7	39·8
Pethidine	10	2	39·7	39·6	39·7	39·5	39·3
Morphine	1	2	40·1	40·0	40·0	40·2	40·3
Morphine	10	2	39·5	39·6	39·8	40·0	40·2
Pentazocine	1	2	39·5	39·3	39·3	39·4	39·3
Pentazocine	10	2	39·7	39·5	39·5	39·4	39·2

rabbits with the lowest dose and in four out of four rabbits with the highest dose.

The rectal temperatures of the pargyline pretreated rabbits given 1 mg/kg of pethidine is shown in Fig. 1. Two rabbits showed only marginal increases in temperature. However, these animals died in hyperthermia when pethidine (2·5

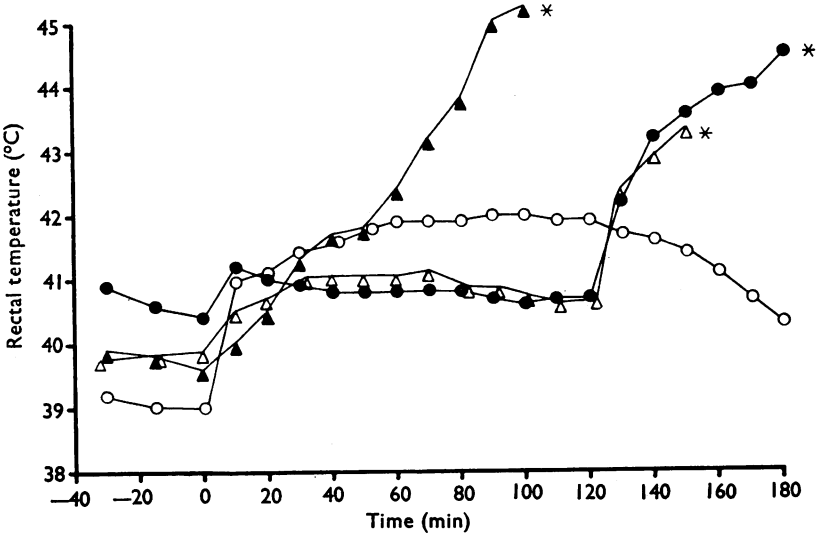

FIG. 1. Effect of pethidine on the rectal temperature of individual rabbits pretreated with pargyline (25 mg/kg s.c. for 5 days). Pethidine (1 mg/kg) was injected intravenously at time zero. Two rabbits (—△— and —●—) were injected with a further intravenous dose of pethidine (2·5 mg/kg) at 120 minutes. Animals that died in hyperthermia are marked *.

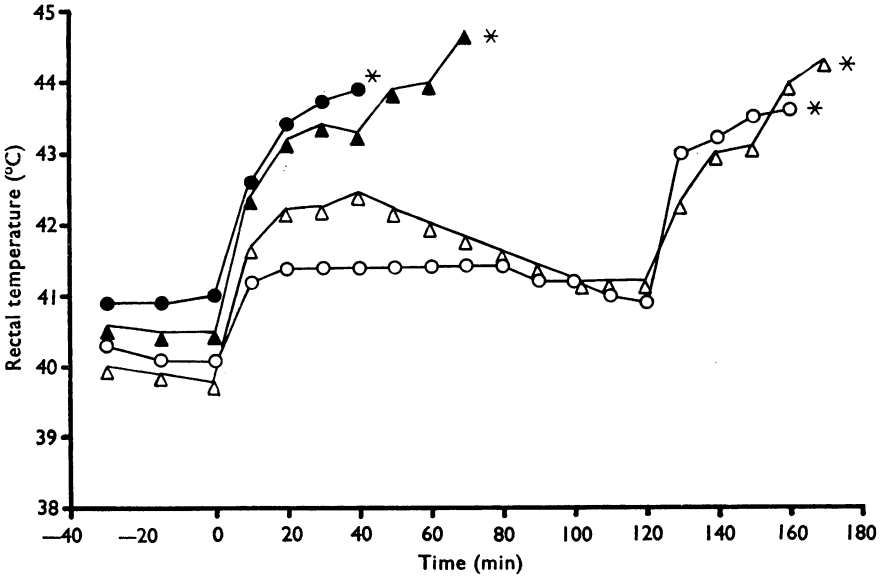

FIG. 2. Effect of pethidine on the rectal temperature of individual rabbits pretreated with pargyline (25 mg/kg s.c. for 5 days). Pethidine (2·5 mg/kg) was injected intravenously at time zero. Two rabbits (—○— and —△—) were injected with a further intravenous dose of pethidine (2·5 mg/kg) at 120 minutes. Animals that died in hyperthermia are marked *.

mg/kg) was injected 2 h after the initial injection, findings which showed the dose-effect relationship and confirmed that the pargyline pretreatment was effective. The results obtained in rabbits given 2·5 mg/kg of pethidine are shown in Fig. 2. Two rabbits did not die after the initial dose of pethidine, even though they showed a temperature rise of more than 1° C; these animals died in hyperthermia after a second dose of pethidine. Figure 3 shows the mean values (±S.E.M.) obtained on the four pargyline pretreated rabbits given 5 mg/kg of pethidine. All died in hyperthermia between 50 and 60 min after injection.

The toxic symptoms of the combination of MAO inhibitor and pethidine were different from those of pethidine alone. In control rabbits pethidine (10 mg/kg) caused little effect on behaviour or rectal temperature (Table 1). When two non-pretreated rabbits were injected intravenously with 50 mg/kg of pethidine, the toxic symptoms consisted of a brief period of clonic convulsions and extensor tonic spasms followed by prostration, respiratory depression and hypothermia (0·5° C in 120 min). In pargyline pretreated rabbits, the pethidine-induced hyperthermia was accompanied by profuse salivation, tremor and motor restlessness.

Morphine

The effect of morphine (1 or 10 mg/kg) on the temperature of rabbits pretreated with pargyline is presented in Fig. 4. One rabbit given the lower dose, although not showing any signs of central excitation, had a delayed hyperthermia and died 3 h after injection. This result is plotted separately. None of the other rabbits receiving morphine showed any significant rise in temperature during the 2 h of observation. Behavioural signs consisted of ataxia and respiratory depression. The

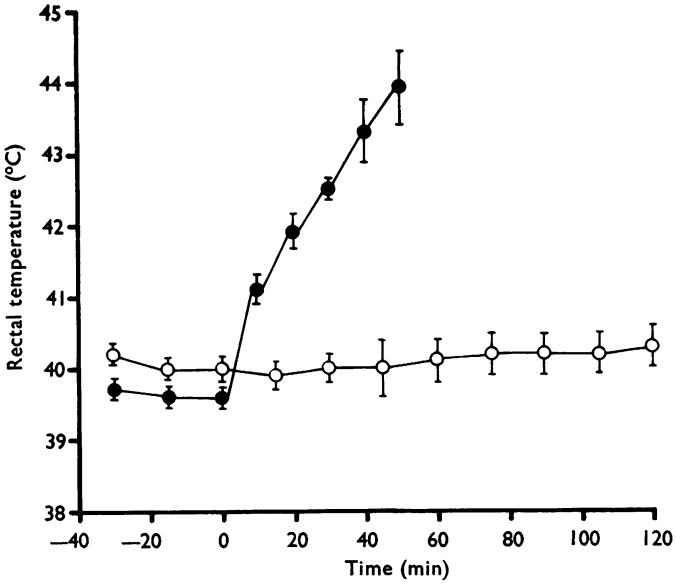

FIG. 3. Effect of 5 mg/kg of pethidine (—●—) and saline (—○—) given by intravenous injection on the rectal temperature of rabbits pretreated with pargyline (25 mg/kg s.c. for 5 days). Injections were made at time zero and each curve represents the mean response from four rabbits. The vertical lines indicate the S.E.M. All the animals receiving pethidine died in hyperthermia.

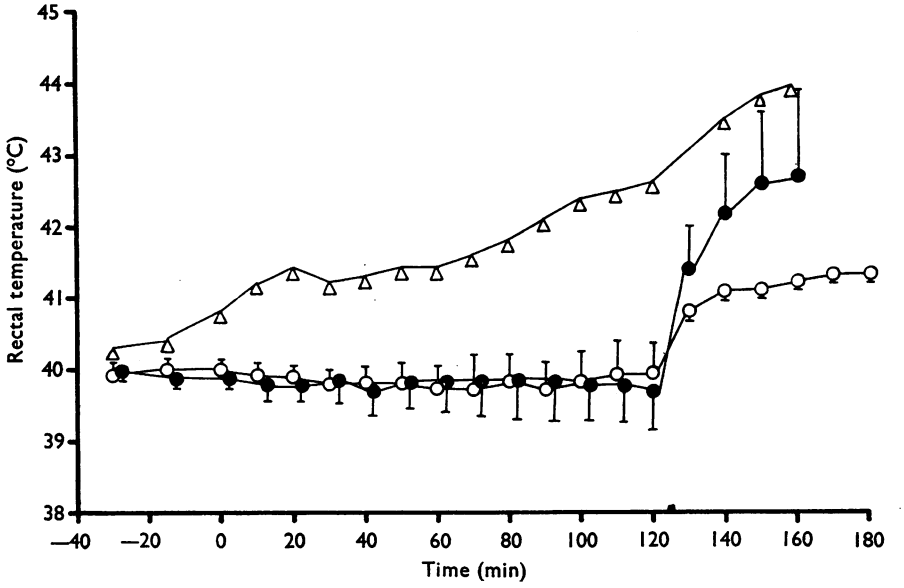

FIG. 4. Effect of an intravenous injection of morphine on the rectal temperature of rabbits pretreated with pargyline (25 mg/kg s.c. for 5 days). —△—, Morphine (1 mg/kg) (one rabbit died 3 h after injection); —○—, morphine (1 mg/kg) (three rabbits); —●—, morphine (10 mg/kg) (four rabbits). The open and closed circles represent mean responses and the vertical lines S.E.M. When these rabbits were given 2·5 mg of pethidine/kg by intravenous injection at 120 min, significant increases of temperature occurred and one of the animals previously given morphine (1 mg/kg) and three of the animals previously given morphine (10 mg/kg) died in hyperthermia.

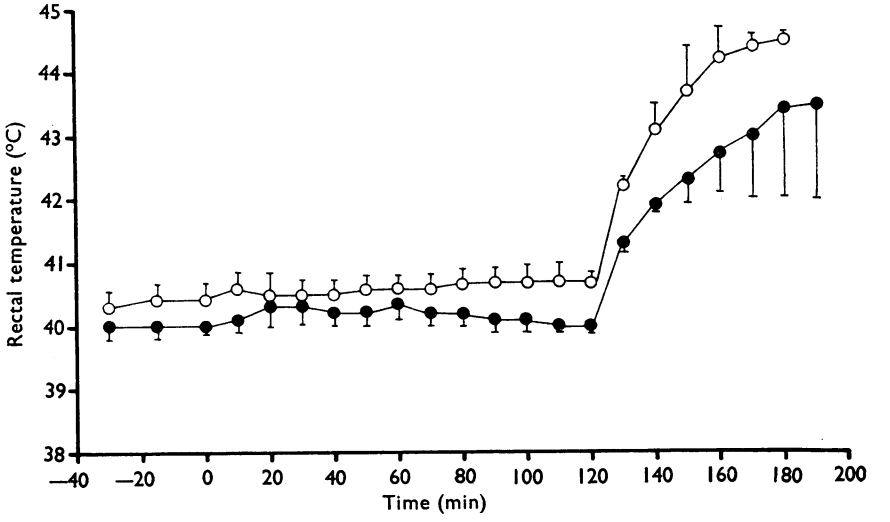

FIG. 5. Effect of 1 mg/kg of pentazocine (—○—) and 10 mg/kg of pentazocine (—●—) injected intravenously on the rectal temperature of rabbits pretreated with pargyline (25 mg/kg s.c. for 5 days). Injections were made at time zero and each curve represents the mean response from four rabbits. The vertical lines indicate the S.E.M. When these rabbits were given 2·5 mg of pethidine/kg by intravenous injection at 120 min, significant increases of temperature occurred and three of the animals previously given pentazocine (1 mg/kg) and one of the animals previously given pentazocine (10 mg/kg) died in hyperthermia.

effectiveness of the pargyline pretreatment was demonstrated by the subsequent injection of 2·5 mg/kg of pethidine. Significant increases in temperature occurred in all of the rabbits given pethidine, and one out of three animals previously given morphine (1 mg/kg) and all three animals previously given morphine (10 mg/kg) died in hyperthermia.

Pentazocine

The effect of pentazocine (1 or 10 mg/kg) on the temperature of pargyline pretreated rabbits is shown in Fig. 5. Pentazocine caused respiratory depression but did not cause any significant change in body temperature over the 2 h of observation. However, there were significant rises in temperature in all of the rabbits subsequently given pethidine (2·5 mg/kg). All three rabbits previously given pentazocine (1 mg/kg) and one out of two of the rabbits previously given pentazocine (10 mg/kg) died from hyperthermia after the injection of pethidine.

Discussion

The experiments reported in this study indicate that potent analgesics other than pethidine are less likely to cause toxic reactions in combination with MAO inhibitors.

In rabbits not pretreated with pargyline, doses of pethidine which were almost lethal (50 mg/kg) failed to cause a significant rise in body temperature, whereas a dose of only 5 mg/kg of pethidine caused a fatal hyperpyrexia in all four rabbits premedicated with pargyline. The rise of body temperature was extremely rapid and increases of 2° C occurred within 10 min of the pethidine injection.

In contrast to the findings with pethidine, the benzomorphan derivative pentazocine in doses of 1 and 10 mg/kg did not cause pyrexia in pargyline pretreated rabbits. Similarly, 10 mg/kg of morphine failed to evoke a toxic reaction. In view of the results with a high dose of morphine, it is difficult to explain why one out of the four rabbits receiving morphine (1 mg/kg) died in hyperthermia (Fig. 4). The body temperature of this animal rose atypically by 0·6° C in the 30 min period allowed for acclimatization to the stocks and continued to rise slowly over the 3 h period following the morphine injection. This response was unlike the response to pethidine but, in the absence of alternative evidence, it must be assumed that the mechanisms involved were similar. The effectiveness of the pargyline pretreatment in rabbits given pentazocine or morphine was verified by the subsequent injection of pethidine which invariably evoked a febrile response.

Brownlee & Williams (1963) reported that the acute toxicity of pethidine in mice was increased by the prior administration of an MAO inhibitor. Further studies with mice have shown that, in addition to pethidine, the acute toxicities of morphine (Mustala & Jounela, 1966) and morphine, pentazocine and phenazocine (Rogers & Thornton, 1969) were also increased and that the lethal effects of the latter three drugs were potentiated by approximately the same degree (Rogers & Thornton, 1969). These findings are in contrast to those of our study on rabbits pretreated with pargyline, in which 5 mg/kg of pethidine was always lethal although pentazocine (10 mg/kg) or morphine (10 mg/kg) failed to induce any increased signs of toxicity. The discrepancy between the results in rabbits and mice may be due to species difference but, in the studies using mice, the animals were given large acute

doses of the MAO inhibitor and not treated chronically. Furthermore, lethal doses of the analgesic drugs were used in the studies on mice whereas the doses used in the present experiments on rabbits were not lethal in the animals not treated with pargyline and were also more closely related to the doses used in man.

The increased toxicity of pethidine in combination with MAO inhibitors has been attributed to a decreased metabolism of the analgesic drug. MAO inhibitors reduce the rate of biotransformation of pethidine, probably by the inhibition of microsomal drug-metabolizing enzymes in the liver (Clark, 1967; Jounela, 1968; Eade & Renton, 1970). This seems unlikely to be the sole mechanism responsible for the drug-drug interaction since in man the reaction occurs within minutes of pethidine administration by the oral or intramuscular routes at a time too short to allow a significant accumulation of the analgesic drug. Furthermore, the symptoms evoked by the interaction between pethidine and pargyline suggest a stimulation of the central nervous system rather than the depression which occurs when detoxification of pethidine is impaired (Dundee & Tinckler, 1952).

There is considerable evidence that the hypothalamic control of body temperature depends upon the relative concentrations or rates of release of 5-hydroxytryptamine (5-HT) and noradrenaline (Feldberg & Myers, 1964). Thus, the febrile response to pethidine may be related to the increased concentration of cerebral monoamines resulting from MAO inhibition. The brain content of noradrenaline and 5-HT is substantially increased in rabbits treated chronically with pargyline (Spector *et al.*, 1963).

Rogers & Thornton (1969) have suggested that the interaction between pethidine and MAO inhibitors may be related specifically to the increased concentration of brain 5-HT. In rabbits, 5-hydroxytryptophan has a pronounced pyretogenic effect (Horita & Gogerty, 1958) which appears to be mediated in the central nervous system (Horita & Hamilton, 1970). Furthermore, there is evidence that the fever caused by bacterial pyrogen is mediated in the rabbit by 5-HT (Canal & Ornesi, 1961; Des Prez, Helman & Oates, 1966).

Carlsson & Lindqvist (1969) have shown that pethidine blocks the neuronal reuptake mechanism for cerebral 5-HT but has little effect on the reuptake mechanism for noradrenaline. Inhibition of reuptake would result in large quantities of extraneuronal 5-HT released from the overloaded storage sites. The fact that morphine and pentazocine show little ability to block neuronal reuptake of 5-HT (Carlsson & Lindqvist, 1969), may explain why these two drugs are less likely to cause a toxic interaction in combination with MAO inhibitors.

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