Title: THE INTERACTIONS OF OPIOIDS AND TRANYLCYPROMINE, AN MAO INHIBITOR

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## INTRODUCTION

The use of monoamine oxidase inhibitors (MAOI) for the treatment of psychiatric illness is undergoing a resurgence in popularity.[1] The potentially lethal clinical interaction between meperidine and various MAOI has been described repeatedly, although the mechanism is not understood. Adverse reactions between morphine and MAOI have also been reported,[2] although these are of questionable validity. There are no clinical or research reports of MAOI-fentanyl interactions. Our objectives were to establish an animal model of meperidine-MAOI interaction and to use this model to evaluate other opioids. The MAOI chosen for study was tranylcypromine sulfate (Parnate©), since the lethal meperidine interaction has been shown to occur in mice treated with this compound.[3]

## METHODS

Male CD-1 mice (35-40 g) were injected subcutaneously with tranylcypromine 20 mg/kg or water (injection volume 0.01 ml/g body weight). This dose of MAOI was previously shown to be nontoxic in these animals. The animals were then placed 5/cage for observation. Room temperature was maintained at 24 ± 1°C. After 4 hours the mice were given subcutaneous injections of opioid: meperidine HCl (50 or 75 mg/kg), morphine sulfate (18.8, 28.3, and 160 mg/kg), fentanyl citrate (0.25 and 0.5 mg/kg), anileridine HCl (10 and 40 mg/kg), and normeperidine HCl (25 and 50 mg/kg). Observations included intermittent measurement of body temperature using a rectal thermistor probe. Lethality was attributed to the drug treatment if death occurred within 24 hours following the opioid.

## RESULTS

Neither tranylcypromine nor any of the opioids given alone caused any obvious toxicity. Animals given tranylcypromine and meperidine showed a dose-related lethal effect (see Table). The animals became hyperactive and died in convulsions, usually within 15-30 minutes of the opioid injection. Body temperatures did not change in a consistent pattern prior to death, although several mice had abrupt 2-3° increases in rectal temperature. These effects could not be demonstrated with morphine or fentanyl. Convulsions and death were produced in one animal by anileridine (a meperidine analogue) and in one animal by normeperidine (a metabolite of both meperidine and anileridine).

## DISCUSSION

This animal model has been used previously,[3] and our results with meperidine confirm the earlier data. The clinical reports of meperidine-MAOI interaction suggest that the phenomenon is real and usually involves hyperpyrexia and convulsions. Both effects were seen in our animals, although the temperature changes were not uniformly present.

The toxic effect does not seem to depend upon opiate receptor interaction. Despite the use of extremely high doses of potent agonists (morphine and fentanyl) no lethality was seen. This gives one hope that no toxicity will occur in humans when these agents are used.

Anileridine and meperidine are metabolized in humans and in the mouse to a convulsant non-narcotic compound, normeperidine. Since we were able to produce a lethal effect with tranylcypromine and the metabolite alone, our data suggest that the toxic syndrome may be due, in part, to normeperidine.

TABLE

(All animals pretreated with tranylcypromine 4 hours before opioid)

| Opioid | Dose (mg/kg) | Number Dead/ Total |
|---|---|---|
| meperidine | 50 | 1/5 |
| meperidine | 75 | 6/10 |
| morphine | 18.8 | 0/5 |
| morphine | 28.3 | 0/5 |
| morphine | 160 | 0/5 |
| fentanyl | 0.25 | 0/5 |
| fentanyl | 0.50 | 0/5 |
| anileridine | 10 | 0/5 |
| anileridine | 40 | 1/5 |
| normeperidine | 25 | 0/5 |
| normeperidine | 50 | 1/5 |

## References

1. Brown TC, Cass NM: Beware -- the use of MAO inhibitors is increasing again. Anesth Intensive Care 7: 65, 1979
2. Vickers MD: Anesthesia and MAO inhibitors. Br Med J 1: 1126, 1965
3. Gessner PK, Clarke CC, Adler M: The effect of low environmental temperature on the tranylcypromine-meperidine interaction in mice. J Pharmacol Exp Ther 189: 90-96, 1974