that in the KA-injected animals the septal cholinergic cells, deprived of the feed-back inhibition, are more sensitive to stimulatory effects of leptazol which probably leads to the greater susceptibility to this convulsant. Atropine reversal of the proconvulsive effect of KA seems to confirm the above hypothesis.

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Effect of monoamine oxidase inhibitors on codeine disposition and pentobarbitone sleep-times in the rat

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Monoamine oxidase inhibitors (MAOIs) have been observed to cause adverse reactions in patients who are also being treated with one of a number of other therapeutic agents (Goldberg 1964; Sjoqvist 1965). Particularly severe reactions have been seen with the analgesic, meperidine, when the MAOI has been phenelzine (Taylor 1962) or pargyline (Vigran 1964).

A degree of controversy has existed over the scientific basis of this particular drug interaction. Various animal studies have shown that meperidine metabolism is inhibited in vitro (Clark 1967; Clark & Thompson 1972) and in vivo (Eade & Renton 1970), and that the LD50 of meperidine in mice was reduced by phenelzine pretreatment (Eade & Renton 1970). Recently, the analgesia caused by meperidine in the rat has been reported to be potentiated by pargyline, and plasma and brain meperidine concentrations and urinary meperidine excretion were significantly higher in pargyline-treated animals (Yeh et al 1979), again indicating alterations in disposition of meperidine. Other reports have concluded that the increased toxicity of potent analgesics in combination with MAOIs is not due to decelerated metabolism of the analgesic, but is related to concentrations of cerebral 5-hydroxytryptamine (Rogers & Thornton 1969; Gessner & Soble 1973). Adverse effects have seldom been observed in patients to whom morphine and MAOIs have been administered concomitantly. However, acute pargyline pretreatment was found to potentiate morphine analgesia in rats (Yeh & Mitchell 1971), probably due to inhibition of morphine glucuronidation (Yeh & Mitchell 1972a), while chronic pargyline pretreatment decreased morphine analgesia probably because of enhanced morphine glucuronidation (Yeh & Mitchell 1972b).

The scope of such interactions between MAOIs and other therapeutic agents has not been explored extensively nor have clinically-meaningful MAOI doses been studied. Consequently, the relevance of these observations to the therapeutic use of MAOIs is difficult to evaluate. The doses which were chosen for study were far in excess of those required to produce 100% inhibition of MAO. This communication presents preliminary results on the interaction of codeine, an analgesic widely prescribed for relief of moderate pain, with various MAOIs which were administered as single doses sufficient for 80% inhibition of MAO (IC80) *in vivo in rats at 1 h after dosing (Leighton et al 1979).* The IC80 for MAO inhibition is thought to correlate with antidepressant efficacy in man (Christmas et al 1972). Data on the interference of these agents with pentobarbitone metabolism, as measured by duration of hypnosis, are also presented. With the exception of clorgyline, the MAOIs studied inhibit non-specifically and irreversibly both A- and B-MAO activity. Clorgyline is a specific, irreversible A-site inhibitor.

Groups of male Sprague-Dawley rats 180–200 g (Charles River Laboratories, N.Y.) were treated with daily injections of 0·9% NaCl (saline) (0·5 ml), tranylcypromine sulphate (2 mg kg^{-1}; Smith Kline and French Labs, Philadelphia, Pa.), clorgyline hydrochloride (2 mg kg^{-1}; May and Baker Co., Dagenham, U.K.), pargyline hydrochloride (20 mg kg^{-1}; Sigma Chemical Co., St. Louis, Mo.) or phenelzine hydrochloride (7 mg kg^{-1}; Warner-Lambert, Ann Arbor, Mi.), all MAOIs being administered i.p. in saline (0·5 ml). One hour after the fifth daily injection, each group of

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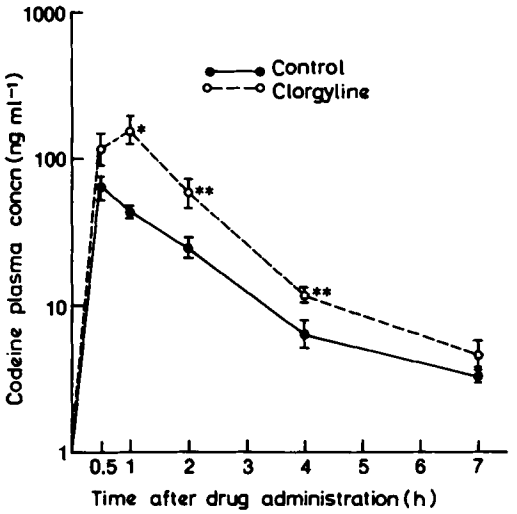

FIG. 1. Plasma codeine concentrations in rats pretreated with saline or clorgyline hydrochloride after administration of 20 mg kg^{-1} codeine (see text for experimental details). Each point represents the mean ± s.e.m. data from 7 rats. * Significantly different, $P = 0.01$, or ** $P = 0.05$, from control data using Student's t-test, one-tailed.

rats received an oral dose of codeine phosphate (equivalent to 20 mg kg^{-1} free base) in saline (0·5 ml) by gavage. One hour after the codeine dose, animals were anaesthetized with chloroform and exsanguinated via the inferior vena cava. Blood was collected into EDTA-containing Vacutainers (Becton-Dickinson Co., Rutherford, N.J.), and plasma was separated by centrifugation and stored at − 20 °C until analysed for codeine content by radioimmunoassay (Findlay et al 1976). In a separate experiment, rats treated as above with saline or clorgyline for 5 days received an oral dose of 20 mg kg^{-1} codeine free base (equivalent) 1 h after the day 5 treatment. Groups of control and clorgyline-treated rats were then killed at 0·5, 1, 2, 4 and 7 h after codeine administration. Blood was collected, and plasma concentrations of codeine were determined as above.

For sleep time experiments, animals were dosed with MAOIs as described for the codeine experiments. One hour following the fifth dose, anaesthesia was induced with sodium pentobarbitone (35 mg kg,$^{-1}$ i.p.). The duration of anaesthesia (sleep time) was determined by the amount of time the animals slept on their backs. An animal was considered awake upon righting three times in 30 s.

Table 1 presents the plasma codeine concentrations in groups of rats on the fifth day of saline or MAOI treatment 1 h after an oral dose of 20 mg kg^{-1} codeine (free base equivalent). Plasma codeine concentrations were significantly higher in all MAOI-treated rats than in saline-treated control animals. Mean concentrations in MAOI-treated rats were approximately 3–7 times higher than that in control animals. The antiserum utilized in this codeine radioimmunoassay does not cross-react with any of the MAOIs used in these experiments, thus eliminating a possible source of error in the higher codeine concentrations reported for treated animals. Norcodeine does have moderate cross-reactivity with this antiserum (Findlay et al 1976), but N-demethylation of codeine in the rat has been reported to be a very minor metabolic pathway (Yeh & Woods 1969).

A separate experiment investigated the effect of clorgyline pretreatment on the oral bioavailability of codeine in the rat. Fig. 1 shows the mean plasma codeine concentrations over the 7 h after oral administration of 20 mg kg^{-1} codeine to groups of rats treated with saline or clorgyline hydrochloride (2 mg kg^{-1}) for 5 days. The mean codeine plasma concentrations in the clorgyline-treated rats were higher at all time points than those in saline-treated animals, and this difference reached significance at 1, 2 and 4 h after codeine administration. The area under the mean curve for clorgyline-treated rats was 2·5 times greater than that for saline-treated animals. Clearly, the oral bioavailability of codeine is increased in rats pretreated with clorgyline relative to saline-treated control animals, although the shapes of the disposition curves in both groups do not suggest a change in drug elimination rate.

Table 2 presents the results of the sleep-time experiments. Tranylcypromine and phenelzine were very effective in potentiating pentobarbitone-induced sleep time. Quite surprisingly, clorgyline was without activity in this test. Preliminary studies indicated that potentiation of sleep time required chronic dosing. A single acute dosing 1 h before pentobarbitone administration was without effect. Also, a single dose of MAOI 24 h before pentobarbitone was without effect. Codeine disposition was not altered by a single administration of MAOI.

Although possible effects of MAOIs on such dispositional parameters as blood flow or renal excretion have not been addressed in the present study, the

Table 1. Plasma codeine concentrations in rats 1 h after an oral dose of 20 mg kg^{-1} codeine free base equivalents (administered as codeine phosphate).

Drug treatment	Codeine concn (ng ml^{-1} (mean ± s.e.m.)
Saline	10·0 ± 2·7 (8)*
Tranylcypromine	57·5 ± 11·9 (8)+
Clorgyline	67·4 ± 10·7 (8)†
Pargyline	42·8 ± 18·4 (8)*
Phenelzine	31·6 ± 2·5 (5)†

* Figure in parentheses indicates number of animals per group.
+ Significantly different from control value $P = 0.01$. Student's t-test, one-tailed.
† Significantly different from control value $P = 0.005$.
* Significantly different from control value $P = 0.1$.

prolongation of pentobarbitone-induced sleep-times suggests that 5-day treatment with a variety of MAOIs interferes with the actual metabolism of codeine and pentobarbitone in rats.

Several differences between the results obtained with codeine and sodium pentobarbitone are apparent. Clorgyline was the most effective agent in potentiating codeine plasma concentrations, but was found to be ineffective in the sleep-time experiments. Also, the relative order of potency in elevating plasma codeine concentrations (clorgyline $\geqslant$ tranylcypromine > pargyline $\geqslant$ phenelzine) was different from the sleep-time experiments (tranylcypromine $\simeq$ phenelzine > pargyline > > clorgyline). The effects on codeine disposition appear to be independent of MAO site inhibition since both A- and B-site inhibitors were effective. In contrast, only B-site inhibitors (not clorgyline) prolonged sleep-time. The data suggest that MAOIs, when given to rats at doses thought to be clinically relevant, have multiple effects, including some on the mixed-function oxidase enzyme systems involved in the metabolism of drugs such as pentobarbitone and codeine. Sufficient data are not available to allow correlation of the effects observed in this report with A- or B-site inhibitors. Studies using additional specific A-site inhibitors would be of value.

Although *N*-demethylation is a minor metabolic pathway in the rat, metabolism by direct conjugation with glucuronic acid and *O*-demethylation to give morphine are major biotransformation pathways (Yeh & Woods 1969). The relative degrees of inhibition of these pathways in MAOI-treated rats and controls should be explored in view of literature reports of differences in effect of pargyline on morphine glucuronidation when the MAOI was administered acutely (Yeh & Mitchell 1972a) or chronically (Yeh & Mitchell 1972b). The effects of MAOIs on the *absolute* oral bioavailability of codeine in the rat should also be studied to seek evidence for the site of inhibition of the drug-metabolizing enzyme system. Presumably this site is in the liver, although effects on gut wall drug-metabolizing enzyme systems cannot be ruled out.

Although rat and man metabolize codeine differently in a quantitative sense, the interaction between MAOIs and codeine suggested by our data is worthy of exploration in the clinical setting where depressed patients may, at times, be receiving therapy with these drugs concomitantly.

Table 2. Effects of MAOIs on pentobarbitone sleeping time in rats.[a]

Drug treatment	Time asleep (min) (mean ± s.e.m.)
Saline	53 ± 6
Tranylcypromine	135 ± 16*
Clorgyline	67 ± 9
Pargyline	92 ± 9*
Phenelzine	134 ± 8*

[a] All experiments involved 8 animals per group.
* Significantly different from control $P = 0{\cdot}001$. Student's *t*-test.

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