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A COMPARISON OF THE EFFECTS OF IMIPRAMINE, TRIMIPRAMINE, AND SOME OTHER DRUGS IN RABBITS TREATED WITH A MONOAMINE OXIDASE INHIBITOR

BY

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The use of monoamine oxidase inhibitors such as, for example, phenelzine, nialamide or tranylcypromine in the treatment of psychiatric depression has led to the occurrence of various severe toxic reactions (Committee on the Safety of Drugs, 1964) in patients undergoing treatment with these drugs when another agent is administered. For convenience these reactions may be divided into two types.

First, hypertensive crises, sometimes with subarachnoid haemorrhage (Blackwell, 1963) or pulmonary oedema (Cuthill, Griffiths & Powell, 1964), may occur when patients have eaten cheese or broad beans (Hodge, Nye & Emerson, 1964) while taking monoamine oxidase inhibitors. It is thought that the high tyramine content of cheese (Asatoor, Levi & Milne, 1963; Blackwell & Marley, 1964; Natoff, 1964) and of 3,4-dihydroxyphenylalanine (dopa) in broad beans (Hodge *et al.*, 1964) may be responsible for these hypertensive effects.

Second, toxic reactions may follow the use of some other centrally acting drug during or shortly after treatment with a monoamine oxidase inhibitor. The drugs implicated in these incompatibilities include imipramine (Davies, 1960; Lee, 1961; Singh, 1960; Luby & Domino, 1961; Brachfield, Wirstshafter & Wolfe, 1963; Stanley & Pal, 1964), amphetamine (Dally, 1962; Mason, 1962; MacDonald, 1963) and pethidine (Taylor, 1962; Palmer, 1960; Shee, 1960; Papp & Benaim, 1958; Denton, Borelli & Edwards, 1962). The symptoms reported usually include hyperexcitement, motor restlessness and hyperpyrexia. In addition to these symptoms, hypertension is a prominent feature in cases where amphetamine is given after a monoamine oxidase inhibitor (Dally, 1962; Mason, 1962).

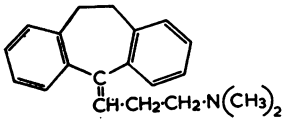
This paper describes some experiments carried out in the rabbit in an attempt to study the toxic interactions between monoamine oxidase inhibitors and other centrally acting drugs, in the hope that the results might be relevant to the clinical use of these drugs and might shed some light on the mechanisms involved.

Potentiation of the acute toxicity of amphetamine and pethidine in mice previously treated with a monoamine oxidase inhibitor (phenelzine) has been reported (Brownlee &

Williams, 1963a, b). However, we have carried out our experiments in the conscious rabbit, partly because of the report (Nymark & Møller-Nielsen, 1963) of the hyperpyrexia produced by the administration of pethidine or amitriptyline to animals previously treated with a monoamine oxidase inhibitor and partly because this enabled us to carry out simultaneous recordings of arterial pressure from the unanaesthetized animal.

In the experiments to be described, we have studied the effects of the administration of a drug to normal rabbits and to rabbits premedicated with a monoamine oxidase inhibitor. The action of imipramine (I) has been compared with that of the chemically related drug trimipramine (II), reported (Lambert & Guyotat, 1961; Lehman & Ban, 1964) to be of value in the treatment of depressive illness, and with the drug amitriptyline (III). The effects of dexamphetamine, pethidine, tyramine, chlorpromazine and trifluoperazine in rabbits premedicated with a monoamine oxidase inhibitor have also been investigated.

(I) —R=H; Imipramine
(II) —R=CH_3; Trimipramine



(III) Amitriptyline

METHODS

Change in rectal temperature

Albino rabbits of either sex and of weight ranging from 2 to 3 kg were treated on two successive days with graded intraperitoneal doses of a monoamine oxidase inhibitor. In all cases the last dose of inhibitor was given at about 4 p.m. On the following day the rabbits were placed in stocks for recording of rectal temperature, and control recordings were taken for 1 to 2 hr before the administration of the second (possibly incompatible) drug. The second drug was infused into a marginal ear vein at a controlled rate of 4.4 mg/min. Rectal temperatures were recorded at 15-min intervals with thermistors (G-23) and a Kent Automatic Recording apparatus. The room temperature was controlled at $25 \pm 1°$ C. In all cases, control untreated animals and controls not previously treated with a monoamine oxidase inhibitor but given the test drug were used. Throughout this paper we use the term hyperpyrexia to denote increases in rectal temperature of more than 3° C.

Blood pressure recordings

In some experiments the blood pressure of the unanaesthetized rabbit was recorded, simultaneously with the rectal temperature, by means of a fine polyethylene cannula inserted into the saphenous artery while the rabbit was anaesthetized with ether (Maxwell & McLusky, demonstration to British Pharmacological Society, Jan., 1964). The cannula was sewn in place and 2 hr were allowed to elapse between the recovery from ether anaesthesia and the recording of rectal temperature and blood pressure. The polyethylene cannula was filled with heparinized saline and led to a Statham P-23G pressure transducer and a pen recorder.

Toxicities

The acute intravenous toxicities of imipramine, trimipramine, amitriptyline, chlorpromazine, trifluoperazine, dexamphetamine and pethidine were determined by infusion into a marginal ear vein of graded doses of the compounds at the rate of 4.4 mg/min to groups of four rabbits per dose. The room temperature was $25 \pm 1°$ C and deaths were recorded up to 24 hr later.

Accurate determinations of the toxicities of the monoamine oxidase inhibitors were not carried out. However, deaths following intraperitoneal administration of graded doses of the drugs on two successive days (that is, under the conditions used for the majority of the experiments) were recorded.

TABLE 1

INCIDENCE OF FATAL HYPERPYREXIA FOLLOWING THE COMBINATION OF A MONOAMINE OXIDASE INHIBITOR AND ANOTHER DRUG

The monoamine oxidase inhibitor was administered intraperitoneally 42 and 18 hr before the slow intravenous infusion of the second drug. Pairs of figures give the number of animals showing fatal hyperpyrexia and the number of animals treated. I.p.=intraperitoneal; i.v.=intravenous. * One additional animal died shortly after trimipramine but did not show any hyperpyrexic response

Monoamine oxidase inhibitor		Incidence of fatal hyperpyrexia after i.v. dose (mg/kg) of										
		Trimipramine			Imipramine		Amitriptyline		Chlor-promazine	Trifluo-perazine	Dexam-phetamine	Pethi-dine
Drug	I.p. dose (mg/kg/day)	5	10	20	5	10	5	10	5	5	2·5	5
Tranylcypromine	50	—	—	—	0/6	4/6	—	—	—	—	—	—
	100	0/6	0/13	0/6*	7/13	6/7	0/6	1/6	0/4	0/4	4/6	4/5
Phenelzine	12·5	—	—		0/2		—	—	—			
	50	0/2	0/9		5/6		11/14	—	0/2			
Nialamide	12·5		—	—	1/2		—				—	—
	50		—	—	2/2		—				—	—
	100		0/4	—	6/6		5/6				4/4	4/5

Drugs

Imipramine, amitriptyline, chlorpromazine, nialamide and tyramine were used as the hydrochlorides; dexamphetamine and tranylcypromine as the sulphates; phenelzine as the dihydrogen sulphate; trifluoperazine as the dihydrochloride, and trimipramine as the maleate. All doses are expressed in terms of the salts, which were dissolved in distilled water or 0.9% saline for injection. Nialamide was used as the base dissolved in an equivalent of hydrochloric acid.

RESULTS

Effects on rectal temperature

Preliminary experiments with rabbits premedicated with a high dose of tranylcypromine indicated that the intravenous administration of imipramine was followed by a considerable increase in rectal temperature in a large proportion of the animals, culminating in death. Hence we compared the actions of imipramine with those of two related antidepressants (trimipramine and amitriptyline) and also studied the effects of dexamphetamine, pethidine, chlorpromazine and trifluoperazine. As examples of monoamine oxidase inhibitors we used the hydrazine derivatives, phenelzine and nialamide, and the non-hydrazine, tranylcypromine.

Preliminary experiments in which tranylcypromine was administered to groups of rabbits for a period ranging from 2 to 9 days, before the infusion of imipramine, indicated that the most clear-cut effects were obtained with animals premedicated 48 and 18 hr previously. Hence, in the experiments described a comparison was made of the effects of the administration of a particular drug to normal rabbits and to rabbits premedicated 48 and 18 hr previously with a monoamine oxidase inhibitor. Table 1 summarizes the results; the pairs

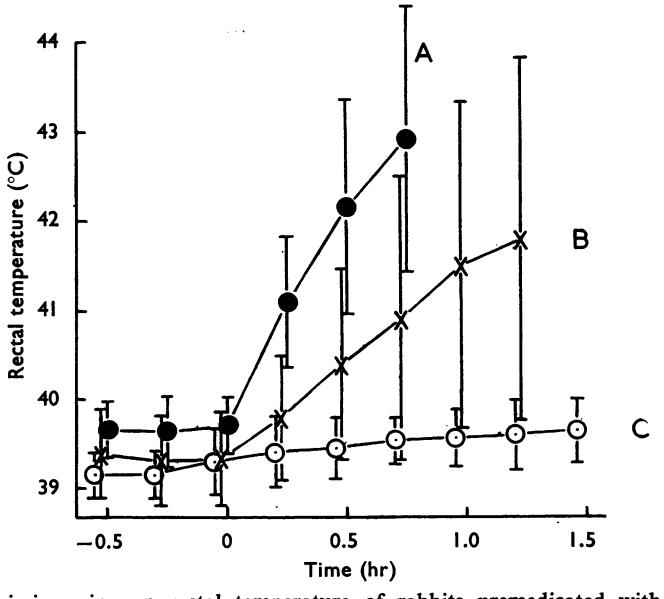


Fig. 1. Effect of imipramine on rectal temperature of rabbits premedicated with tranylcypromine. Animals in (A) and (B) were given tranylcypromine (100 mg/kg, intraperitoneally) 42 and 18 hr before intravenous administration of imipramine at zero time. Points refer to means and vertical lines to the standard deviations. (A) Imipramine, 10 mg/kg (four rabbits); (B) imipramine, 5 mg/kg (thirteen rabbits); (C) imipramine, 10 mg/kg (five non-premedicated animals).

of figures give the numbers of animals that died in hyperpyrexia following the administration of the second (possibly incompatible) drug and the numbers of animals tested.

The effects of the intravenous administration of imipramine (10 mg/kg) to normal rabbits and of 5 or 10 mg/kg of imipramine to animals previously treated on the two successive days with 100 mg/kg of tranylcypromine are shown in Fig. 1. Animals not premedicated with tranylcypromine but given 5 or 10 mg/kg of imipramine showed no significant change in rectal temperature and their behaviour remained apparently normal. In contrast, those that had received tranylcypromine (two doses of 100 mg/kg, intraperitoneally) showed a rise in rectal temperature following imipramine, which was more rapid after 10 mg/kg than 5 mg/kg and was accompanied by symptoms of hyperexcitement, tremor, increased reactivity and motor restlessness. A large proportion of the rabbits died 1 to 2 hr after administration of imipramine, when the rectal temperature had reached 43 to 44° C. In thirteen animals treated with tranylcypromine (two doses of 100 mg/kg) and imipramine (5 mg/kg) there were seven deaths and eight rabbits showed a rise of rectal temperature of more than 1.5° C. The remaining five animals showed little response. Following either dose of imipramine death was almost invariably associated with hyperpyrexia. There is thus some evidence that when a rise of rectal temperature of more than 1.5° C occurred it was usually followed by a continued increase terminating in death. No hyperpyrexia was observed in the animals to which only one of the two drugs (tranylcypromine or imipramine) was administered; the reaction only occurred when both drugs were administered.

A similar hyperpyrexial response terminating in the death of the rabbit was observed following the administration of imipramine (5 mg/kg, intravenously) to rabbits premedicated on two successive days with phenelzine (50 mg/kg, intraperitoneally) or nialamide (50 or 100 mg/kg, intraperitoneally). Lower doses of either phenelzine or nialamide produced a less consistent hyperpyrexial reaction.

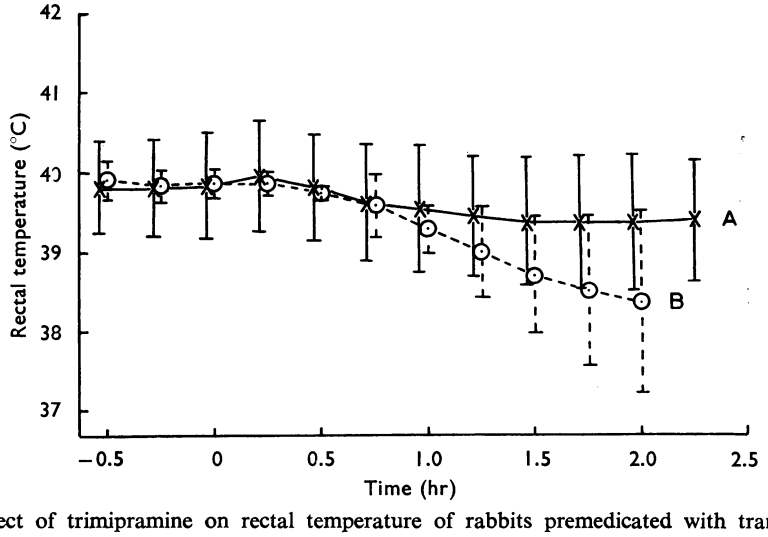


Fig. 2. Effect of trimipramine on rectal temperature of rabbits premedicated with tranylcypromine. Animals were given tranylcypromine (100 mg/kg, intraperitoneally) 42 and 18 hr before the administration of trimipramine at zero time. Points refer to the means and the vertical lines to the standard deviations. (A) Trimipramine, 10 mg/kg (eight rabbits); (B) trimipramine, 20 mg/kg (four rabbits).

In contrast to these effects of imipramine, we unexpectedly found that the chemically and pharmacologically related drug, trimipramine, in intravenous doses of 5, 10 or 20 mg/kg, did not produce any significant rise in rectal temperature (Fig. 2) in rabbits premedicated with any one of the three monoamine oxidase inhibitors (Table 1). There appeared to be a reduction in the rectal temperature of the rabbits after 20 mg/kg of trimipramine (Fig. 2), and the behaviour of the treated animals remained nearly normal. One animal receiving 20 mg/kg died a few minutes after administration; this animal had no rise in rectal temperature, and it appears likely that death was due to the high dose of trimipramine used (intravenous LD50=27 mg/kg). With amitriptyline (Table 1; Fig. 3) there was a difference

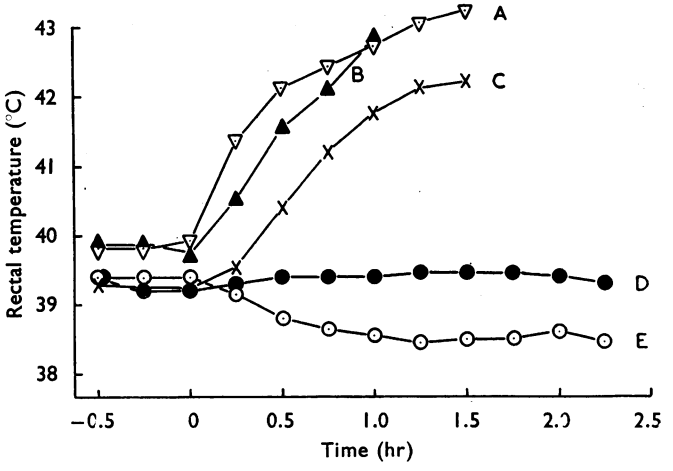


Fig. 3. Effect of intravenous administration of a second drug on the rectal temperature of rabbits premedicated 42 and 18 hr previously with a monoamine oxidase inhibitor. (A) Dexamphetamine, 2.5 mg/kg (four rabbits); (B) pethidine, 5 mg/kg (four rabbits); (C) amitriptyline, 5 mg/kg (four rabbits); (D) amitriptyline, 5 mg/kg (four rabbits); (E) trifluoperazine, 5 mg/kg (four rabbits). In (A), (B), (D), and (E) the monoamine oxidase inhibitor was tranylcypromine (100 mg/kg, intraperitoneally), and in (C) phenelzine (50 mg/kg, intraperitoneally).

in the incidence of the hyperpyrexial response according to which monoamine oxidase inhibitor was used. Although only one fatal hyperpyrexial response occurred in twelve animals after premedication with tranylcypromine, a hyperpyrexial response occurred in eleven of fourteen animals premedicated with phenelzine and five of six rabbits premedicated with nialamide. In contrast, a high incidence of fatal reactions occurred with imipramine when used in conjunction with any one of the three monoamine oxidase inhibitors tested, whilst trimipramine produced no fatal reactions with any inhibitor used.

Both pethidine and dexamphetamine produced fatal hyperpyrexia in a high proportion of rabbits premedicated with tranylcypromine (Fig. 3) or nialamide (Table 1). No hyperpyrexia or death was produced in rabbits given chlorpromazine (5 mg/kg, intravenously) after phenelzine or tranylcypromine (Table 1) or in rabbits given trifluoperazine (5 mg/kg, intravenously) after tranylcypromine.

Blood pressure experiments

A small number of experiments were carried out in which the arterial (saphenous) pressure of the rabbit was recorded simultaneously with the rectal temperature. In three

experiments (Fig. 4,A) imipramine was administered intravenously to animals premedicated with tranylcypromine. The rise in rectal temperature normally observed under these conditions was recorded but there was no significant change in arterial pressure. In contrast, the intravenous infusion of tyramine (2.5 mg/kg) into rabbits premedicated with tranylcypromine, under identical conditions, was followed by a rise in arterial pressure accompanied by only a moderate increase in rectal temperature from which the animals survived (Fig. 4,B).

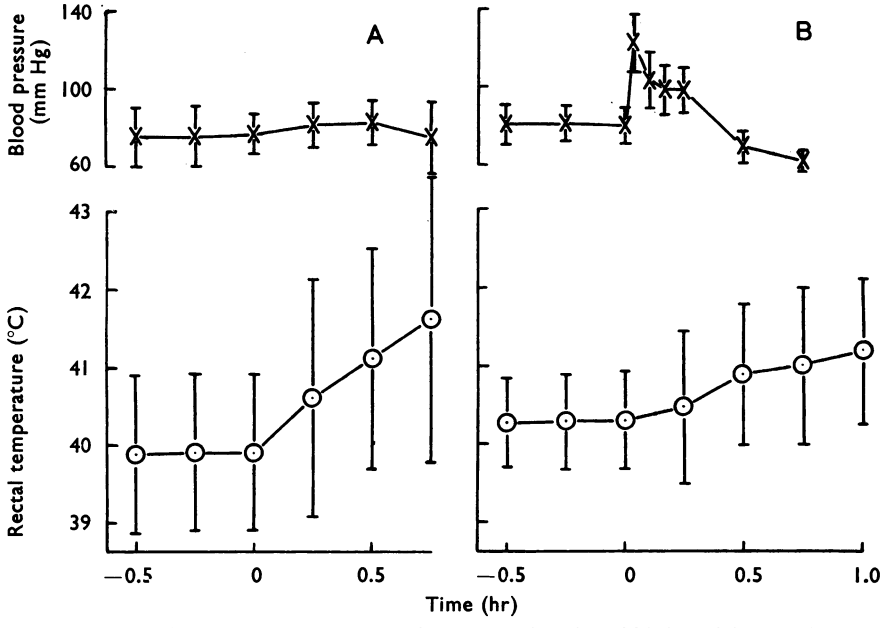


Fig. 4. The effect of (A) imipramine (5 mg/kg, intravenously; six rabbits) or (B) tyramine (2.5 mg/kg, intravenously; three rabbits) injected at zero time, on arterial pressure and rectal temperature of conscious rabbits premedicated with tranylcypromine (100 mg/kg, intraperitoneally) 42 and 18 hr previously. The upper curves refer to the mean saphenous pressure taken as diastolic pressure plus one-third pulse pressure, and the lower curves to the mean rectal temperature. Vertical lines are standard deviations.

Acute toxicities

The acute toxicities of the various drugs used in these experiments, determined by the routes and under conditions similar to those used in the incompatibility experiments, are set out in Table 2. The deaths following imipramine usually occurred during or shortly after infusion of the drug and were associated with respiratory depression, loss of muscle tone, slight motor stimulation, convulsive movements and only slight (about 1° C) increase in the rectal temperature. This is to be contrasted with the hyperpyrexia and the delay of 1 or 2 hr in deaths following the administration of lower doses of imipramine to rabbits premedicated with appropriate doses of a monoamine oxidase inhibitor. The acute toxic symptoms following trimipramine administration to unpremedicated rabbits were similar to those of imipramine except there was no evidence of stimulation and there was slight hypothermia (about 1° C) rather than pyrexia. No severe toxic symptoms were observed with intravenous pethidine up to 40 mg/kg, the most prominent symptom being respiratory

TABLE 2

ACUTE TOXICITIES IN THE RABBIT OF DRUGS USED IN THE INCOMPATIBILITY EXPERIMENTS

The drugs administered intravenously (i.v.) were infused at a rate of 4·4 mg/min to rabbits restrained in a stock and kept at 25±1° C. Deaths were recorded for 24 hr later. The monoamine oxidase inhibitors were administered intraperitoneally (i.p.) to groups of four rabbits on two successive days and deaths were recorded for a further 3 days. The figures in the brackets are the 95% fiducial limits

Compound	Route	LD50 (mg/kg)
Imipramine	I.v.	30 (28–33)
Trimipramine	I.v.	27 (25–30)
Amitriptyline	I.v.	21 (16·6–26·8)
Chlorpromazine	I.v.	40 (29–55)
Trifluoperazine	I.v.	65 (51–82)
Pethidine	I.v.	>40
Dexamphetamine	I.v.	15 (11·5–19·5)
Tranylcypromine	I.p.	150
Nialamide	I.p.	>150
Phenelzine	I.p.	70

depression. There was no significant increase in rectal temperature. Amphetamine in toxic doses produced excitement, motor restlessness and some hyperpyrexia.

The toxicity values for the monoamine oxidase inhibitors in the rabbit are only approximate, but are included to indicate the closeness of the dose required to produce a hyperpyrexia with imipramine and the toxic dose.

DISCUSSION

The primary purpose of the experiments reported here was to study, in experimental animals, the toxic interaction between monoamine oxidase inhibitors and other centrally acting drugs reported to produce severe reactions when administered to patients during or shortly after treatment with a monoamine oxidase inhibitor.

The drugs (imipramine, amphetamine and pethidine) that have been reported to produce a severe reaction with monoamine oxidase inhibitors in man cause hyperpyrexia in the rabbit, and, conversely, the drug trifluoperazine, which has been associated with the monoamine oxidase inhibitor tranylcypromine (for example in Parstelin) without any apparent increase in toxicity of the latter, does not produce hyperpyrexia when administered to rabbits premedicated with a monoamine oxidase inhibitor. Furthermore, symptoms of hyperexcitement and hyperpyrexia are reported to occur in man following the inadvertent administration of imipramine to patients under treatment with a monoamine oxidase inhibitor (Davies, 1960; Stanley & Pal, 1964), and this is the type of toxic reaction seen in the rabbit.

Our results show that not all iminodibenzyl antidepressant drugs produce a hyperpyrexial response in rabbits premedicated with a monoamine oxidase inhibitor. The drug trimipramine, chemically closely related to imipramine and reported (Lambert & Guyotat, 1961; Lehmann & Ban, 1964) to have clinical antidepressant properties somewhat similar to those of imipramine, did not produce hyperpyrexia in the rabbit in intravenous doses ranging from 5 to 20 mg/kg after any of the three monoamine oxidase inhibitors tested, whilst imipramine in doses of 5 or 10 mg/kg produced hyperpyrexia in a high proportion of rabbits previously treated with each of these same three drugs.

Amitriptyline, also clinically useful in the treatment of depressive illness and with chemical and pharmacological similarities to imipramine (Vernier, 1961; Vernier, Hanson & Stone, 1962), produced a fatal hyperpyrexial response in only one of twelve rabbits premedicated with tranylcypromine. Eleven of fourteen animals treated with phenelzine and five of six treated with nialamide showed hyperpyrexia terminating in death following 5 mg/kg of amitriptyline.

These experiments bring out an important qualitative difference between these three imipramine-like antidepressant drugs (imipramine, trimipramine and amitriptyline), which otherwise appear to have only quantitative differences. Imipramine was the only one of the three drugs which consistently caused a toxic hyperpyrexial response following a monoamine oxidase inhibitor in the rabbit. However, in this species, and under the same conditions of administration, the three drugs have similar stimulant potencies in reversing reserpine- or chlorpromazine-induced ptosis (Maxwell, 1964; Table 3), and have similar acute toxicities.

TABLE 3

COMPARISON IN THE RABBIT OF THE STIMULANT OR ANTIDEPRESSANT ACTIONS OF IMIPRAMINE-LIKE DRUGS WITH THE INCIDENCE OF FATAL HYPERPYREXIA IN ASSOCIATION WITH TRANYLCYPROMINE

Data for the reserpine and chlorpromazine reversal activities are quoted from Maxwell (1964). Figures refer to the mean and standard deviation and the number of experiments in parentheses. The incidence of fatal hyperpyrexia is from Table 2, and LD50s are from Table 3. The incidence of fatal hyperpyrexia refers to rabbits premedicated on two successive days with 100 mg/kg of tranylcypromine and then given intravenously 10 mg/kg of the second drug

Second drug	Effective i.v. dose (mg/kg) for: Reserpine reversal	Chlorpromazine reversal	LD50	Incidence of fatal hyperpyrexia
Imipramine	12·7±1 (5)	16·2±2 (4)	30	6/7 =86%
Amitriptyline	9·7±4 (3)	10·9±1 (2)	21	1/6 =17%
Trimipramine	16·7±1 (8)	13 ±1 (2)	27	0/13= 0%

The doses of the monoamine oxidase inhibitors required to produce fatal hyperpyrexia with imipramine or amitriptyline were high, near to toxic levels, and considerably greater than those required to produce *in vivo* inhibition of monoamine oxidase in the rat (Pletscher, Gey & Zeller, 1960) or to potentiate the action of tryptamine in mice (Maxwell, Gray & Taylor, 1961) or 5-hydroxytryptamine in the rabbit (Horita, 1959).

We have no direct information on the mechanism whereby the hyperpyrexial response to the combination of monoamine oxidase inhibitors and imipramine, amphetamine or pethidine is produced, but there are a number of possible explanations.

Inhibitors of monoamine oxidase are known to have pharmacological and biochemical actions unrelated to inhibition of monoamine oxidase (Laroche & Brodie, 1960; Burford, Leick & Walaszek, 1960). For example, iproniazid and pheniprazine (Fouts & Brodie, 1956; Serrone & Fujimoto, 1960) prolong barbiturate anaesthesia in mice and rats and it is thought (Laroche & Brodie, 1960) that this is due to an effect on liver microsomal enzymes responsible for the metabolic inactivation of hexobarbitone. One possibility, therefore, is that the hyperpyrexial reactions are due to inhibition, by the monoamine oxidase inhibitors, of the enzymes responsible for the metabolic inactivation of imipramine, amphetamine or pethidine. If this were indeed the case, one might expect that the toxic symptoms observed due to the combination of monoamine oxidase inhibitor and, for example, imipramine,

would be similar to that of a higher dose of the second drug. In fact, the toxic symptoms of the combination of monoamine oxidase inhibitor and imipramine or pethidine are different from that of imipramine or pethidine alone. Death after high dose of imipramine, in the rabbit, is due primarily to respiratory depression and is associated with mild (1° C) hyperpyrexia, and there is little excitation. In contrast, the combination of imipramine and a monoamine oxidase inhibitor produces symptoms (such as hyperpyrexia, hyperexcitement and tremor) not observed following any dose of imipramine alone.

Another possibility is that the monoamine oxidase inhibitors act on the liver enzymes in such a manner as to alter the route of metabolic inactivation of the compounds and that the resulting abnormal metabolites have a common pharmacological action.

An alternative and, to us, more likely explanation is related to the enhancement of a physiological action of catechol or indole amines in the central nervous system. The administration of the monoamine oxidase inhibitors iproniazid (Brodie, Spector & Shore, 1959) or pargyline (Spector, 1963) causes an increase in the brain levels of both noradrenaline and 5-hydroxytryptamine in the rabbit. Similar increases in the brain levels of noradrenaline or 5-hydroxytryptamine in the brain of the mouse and rat have been reported with the monoamine oxidase inhibitors used in our experiments (Crout, Creveling & Udenfriend, 1961; Green & Erickson, 1960; Göschke, 1961).

Although we have made no determinations of brain levels of 5-hydroxytryptamine or noradrenaline under the conditions we have used to study the incompatibility with other drugs, it appears likely that, under the conditions and with the monoamine oxidase inhibitors we have employed, the brain levels of noradrenaline and 5-hydroxytryptamine were above normal before the administration of the second drug (such as imipramine).

Imipramine is not an inhibitor of brain monoamine oxidase (Pulver, Exer & Herrmann, 1960) nor is its desmethyl derivative (Sulser, Bickel & Brodie, 1964) which is thought (Sulser, Watts & Brodie, 1962) to be responsible for its clinical antidepressant action. Similarly, neither imipramine nor desmethylimipramine alter the brain levels of noradrenaline or 5-hydroxytryptamine in the rat (Sulser *et al.*, 1962).

The mechanism whereby imipramine exerts its clinical antidepressant action is unknown. Imipramine and amitriptyline are known to potentiate and prolong the action of noradrenaline or of 5-hydroxytryptamine on the blood pressure and nictitating membrane of the cat (Sigg, 1959, 1962; Schaeppi, 1960) and to potentiate the pressor response to noradrenaline in the dog (Halliwell, Quinton & Williams, 1964). Trimipramine potentiates the effects of noradrenaline or 5-hydroxytryptamine on the cat nictitating membrane less consistently than imipramine (Loveless & Maxwell, unpublished).

Amphetamine is thought to cause release of noradrenaline from peripheral sites (Burn & Rand, 1958) and has been claimed to sensitize the reticular activating system to the alerting effects of adrenaline (Hiebel, Bonvallet, Huvé & Dell, 1954; Rothballer, 1957). We have found no information on the effects of pethidine on brain levels of noradrenaline or 5-hydroxytryptamine.

It is possible that the combination of a high dose of monoamine oxidase inhibitor and of imipramine or amphetamine would cause the enhancement of the action of catechol or indole amines in the central nervous system, either by causing further release of these amines from their binding sites (amphetamine) or by augmenting the action of the amines

already present (imipramine). Cooper, Cranston & Honour (1964) have shown that the administration of 5-hydroxytryptamine into the lateral ventricle of the rabbit either caused a fall in rectal temperature or was without effect. The intraventricular administration of noradrenaline, in contrast, produced either a rise in rectal temperature or no effect. These results are diametrically opposed to those found in the cat by Feldberg & Myers (1964). If imipramine or amphetamine augmented the central actions of the increased brain levels of noradrenaline or 5-hydroxytryptamine produced in the rabbit by the monoamine oxidase inhibitor treatment, this might result in a hyperpyrexial response. It is, furthermore, possible that the difference between the effects of imipramine and trimipramine, in association with monoamine oxidase inhibitors in the rabbit, is related to a difference in their abilities to enhance the effects of 5-hydroxytryptamine as compared with noradrenaline.

The difference between the effects on arterial pressure of imipramine and tyramine, in animals previously treated with a monoamine oxidase inhibitor, is interesting, and suggests that the toxic effects of imipramine following monoamine oxidase inhibitors are predominantly central in origin with little effect on the peripheral circulation. In the case of tyramine, we find a marked rise in arterial pressure and a slight increase in rectal temperature, which suggests that the toxic reactions due to the ingestion of foods, containing a high tyramine content, by patients being treated with monoamine oxidase are partly due to a peripheral action on arterial pressure and partly to a central effect.

SUMMARY

1. The effects of the intravenous infusion of imipramine, trimipramine, amitriptyline, dexamphetamine, pethidine, chlorpromazine, trifluoperazine or tyramine into unanaesthetized rabbits premedicated with tranylcypromine, phenelzine or nialamide have been studied.

2. The administration of imipramine to rabbits premedicated with tranylcypromine, nialamide or phenelzine was followed by a marked and fatal hyperpyrexial response in a large proportion of the animals.

3. The administration of trimipramine to rabbits previously treated with the same three monoamine oxidase inhibitors was not followed by hyperpyrexia or death.

4. The administration of amitriptyline to rabbits previously treated with phenelzine or nialamide caused a high incidence of fatal hyperpyrexial responses, but there was a low incidence of hyperpyrexia with amitriptyline administered to rabbits premedicated with tranylcypromine.

5. Fatal hyperpyrexia was also produced in a large proportion of rabbits premedicated with tranylcypromine or nialamide and given dexamphetamine or pethidine.

6. Fatal hyperpyrexia was not produced by the administration of chlorpromazine to rabbits previously treated with tranylcypromine or phenelzine, or by trifluoperazine to rabbits premedicated with tranylcypromine.

7. Hyperpyrexia produced by imipramine in rabbits premedicated with tranylcypromine was not accompanied by any significant change in arterial pressure of the unanaesthetized rabbit, whilst the administration of tyramine to rabbits premedicated with tranylcypromine caused a marked rise in arterial pressure and only a slight rise in rectal temperature.

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