**Interactions of monoamine oxidase inhibition and sympathomimetic amines on the human iris.**

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Monoamine oxidase (MAO) is the term used to designate a group of enzymes catalysing the deamination of tyramine, 5-hydroxytryptamine, noradrenaline and other monoamines. Brain MAO in man consists of a group of at least four conformational isoenzymes (Collins, Sandler, Williams & Youdin, 1970) which can be classified according to the differing sensitivity of the constituent parts to various MAO inhibitors.

In this series of experiments, we have investigated the interaction of two hydrazine MAO inhibitors, iproniazid and isocarboxazid, and of clorgyline [*N*-methyl-*N*-propargyl-3(2,4 dichlorophenoxy) propylamine, M & B 9302], a new MAO inhibitor (Johnston, 1968), with three sympathomimetic amines on the human iris, using the photographic technique of Sneddon & Turner (1969). In Table 1 the mydriatic responses of depressed patients controlled on one of the two hydrazine compounds are compared with those of an untreated control group of depressed subjects.

TABLE 1. *The effect of hydrazine MAO inhibitors on the mydriatic response, at 30 min to sympathomimetic amines*

| | Untreated | | Treated | | | |
|---|---|---|---|---|---|---|
| | *n* | % mydriasis ± S.E.M. | *n* | % mydriasis ± S.E.M. | Difference | *P* |
| Tyramine 2·0% | 46 | 33·0 ± 4·2 | 12 | 79·7 ± 6·9 | +46·7 | <0·001 |
| Hydroxyamphetamine 1·0% | 10 | 60·5 ± 5·9 | 4 | 91·5 ± 4·6 | +31·0 | <0·01 |
| Phenylephrine 5·0% | 25 | 25·0 ± 3·9 | 11 | 26·0 ± 6·8 | +1·0 | N.S. |

Clorgyline, which is reported to have a differential activity on different parts of the MAO complex (Hall, Logan & Parsons, 1969), potentiated the response to tyramine (20 mg/ml) by 39·7% ($P<0·001$), and to hydroxyamphetamine (10 mg/ml) by 24·1% ($P<0·05$) but did not change that to phenylephrine (50 mg/ml). Clorgyline also significantly potentiated the pressor response to 5 mg phenylpropanolamine given orally.

The photographic technique used has the advantage that enzyme systems in the liver and intenstine are not involved. Therefore, any potentiation seen in the mydriatic response to sympathomimetic amines must be due primarily to an action on the sympathetic nerve terminals of the dilator pupillae. The directly acting sympathomimetic amine, phenylephrine, though a substrate for MAO, was not potentiated in this situation by any of the MAO inhibitors used. Both of the indirectly acting amines were potentiated, however, though hydroxyamphetamine is not a substrate for MAO.

This would suggest that at least part of the potentiation of the action of sympathomimetic amines seen after MAO inhibition is due to the greater availability of the transmitter in the sympathetic neurones of subjects treated with an MAO inhibitor. Inhibition in the liver and intestine may also be a contributing factor following oral or intravenous administration of sympathomimetic amines.

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## Method of studying anticonvulsant properties of drugs in man

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The efficacy of anticonvulsant drugs is commonly assessed by observing their effect upon the convulsive threshold in experimental animals; it is clearly unacceptable to use this method of evaluation in man. However, the use of flurothyl as a therapeutic convulsant for the treatment of patients suffering from endogenous depression affords a means of observing the effect of drugs upon a seizure in progress.

Flurothyl (Indoklon: Ohio Chemical Co.) is a hexa-fluoryl-diethyl-ether; administered by inhalation it causes reproducible grand mal seizures in animals and man in concentrations as low as 32 parts per million (Krantz, Truitt, Speers & Ling, 1957). The epileptiform response occurs in three distinct phases; there is a preliminary myoclonic phase of irregular movements which is succeeded by tonic and clonic phases similar to those in electro-convulsive therapy (ECT), the tonic lasting for about 15 s and the clonic of varying duration but much longer than that seen with ECT. Establishment of the tonic phase is invariably followed by the clonic and may be regarded as the criterion of a successful treatment.

In these studies each subject was his own control, and since in a series of treatments the duration of the seizure progressively diminishes (Ottosson, 1960), the drug under test was given at the patient's third treatment and control observations made on the next, that is shorter, convulsion. The techniques of anaesthesia and administration of the standard dose of flurothyl (0·35 ml) with oxygen as the carrier gas have been described in detail by Rose & Watson (1967). At the onset of the tonic phase the test drug was given rapidly into an antecubital vein. Cerebral activity and heart-rate were monitored throughout on a Grass polygraph; in some cases, after the induction of anaesthesia, blood pressure was monitored by percutaneous puncture of a radial artery. Times were marked on the polygram of the administration of all drugs and of the clinical observation of anaesthesia, depolarization, phases of the seizure and post-ictal waking.

Anticonvulsants were not used more than twice in the course of any patient's treatment for depression, and we have no evidence that recovery from this illness was in any way prejudiced.

Our results will be published elsewhere (Watson, Harrison & Rees, 1970), but in summary, diazepam 15 mg, nitrazepam 15 mg and thiopentone sodium 250 mg all produced marked reduction in the length of seizures. An example of polygraphic records on test and control days in the same patient will be shown.

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