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Comparison of the effects of chronic administration of ciclazindol and desipramine on pupillary responses to tyramine, methoxamine and pilocarpine in healthy volunteers

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1 Twenty-nine healthy volunteers participated in an experiment lasting for 8 weeks: Phase I (2 weeks)—pre-treatment control period; Phase II (4 weeks)—medication with either ciclazindol hydrochloride (50 mg twice daily), or desipramine hydrochloride (50 mg twice daily) or lactose placebo (twice daily) administered in a single-blind fasion; Phase II (2 weeks)—recovery.

2 Experimental sessions took place twice weekly for the photographic assessment of resting pupil diameter, and for the assessment of one of the following pupillary responses: mydriatic response to methoxamine, mydriatic response to tyramine, miotic response to pilocarpine.

3 Resting pupil diameter increased during medication with either ciclazindol or desipramine.

4 Methoxamine-evoked mydriasis and tyramine-evoked mydriasis were antagonized by both ciclazindol and desipramine.

5 Pilocarpine-evoked miosis was potentiated by both ciclazindol and desipramine.

6 The steady-state plasma levels (mean ± s.e. mean) of the antidepressants were: ciclazindol: 5.90 ± 0.74 μM; desipramine: 0.60 ± 0.17 μM.

7 The antagonism of methoxamine-evoked mydriasis is likely to reflect the blockade of postsynaptic α_1-adrenoceptors in the iris by the antidepressants, whereas the antagonism of tyramine-evoked mydriasis may reflect both the blockade of uptake of tyramine into presynaptic adrenergic terminals and the blockade of postsynaptic α-adrenoceptors. There is no immediate explanation for the potentiation of pilocarpine-evoked miosis by the two antidepressants.

Keywords ciclazindol desipramine pupil methoxamine tyramine pilocarpine

Introduction

Ciclazindol, 10-(*m*-chlorphenyl)-2,3,4,10-tetrahydro-pyrimidol (1,2α)indol-10-ol (Swaisland *et al.*, 1977; Kirby & Turner, 1977) is a tetracyclic compound with activities very similar to those of established tricyclic antidepressants in animal tests used to detect potential antidepressant activity. Similarly to imipramine, ciclazindol antagonizes reserpine- and tetrabenazine-induced hypothermia in mice, potentiates metamphetamine-induced weight loss in

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rats, and potentiates the noradrenaline-induced pressor response and the electrically induced contractions of the nictitating membrane in cats (Beckett *et al.*, 1973). Furthermore, ciclazindol is a potent blocker of the uptake of noradrenaline into brain slices, with little affinity for the 5-hydroxytryptamine uptake mechanism (Sugden, 1974). In contrast to established tricyclic antidepressants (imipramine, desipramine, nortriptyline, amitriptyline), ciclazindol has no significant antimuscarinic, α-adrenoceptor blocking, anti-5-hydroxytryptamine, and anti-histamine properties (Waterfall *et al.*, 1979). A preliminary clinical trial supports predictions from preclinical studies that ciclazindol may be a clinically effective antidepressant with few autonomic side-effects (Ghose *et al.*, 1978). Furthermore, it has recently been reported that ciclazindol may have additional clinical usefulness as an anorectic and hypoglycaemic agent (Lean & Borthwick, 1983).

Although observations in isolated tissue preparations can be used as predictors of the possible autonomic effects of drugs in humans, it is necessary to establish whether the predicted effects occur in humans treated with clinically relevant doses of the drugs in question. The human iris seems to be a particularly suitable pharmacological test system to study the effects of drugs acting on the autonomic nervous system. The iris is innervated by both adrenergic and cholinergic fibres, and the response of this tissue to topically applied agonists can easily be measured as a change in the diameter of the pupil. This method has already been used successfully to demonstrate the actions of conventional tricyclic antidepressants on the autonomic nervous system. Thus, it has been shown that desipramine and amitriptyline can antagonize the miosis evoked by pilocarpine (Szabadi *et al.*, 1980), and the mydriasis evoked by tyramine (Szabadi *et al.*, 1975; Ghose, 1976; Shur & Checkley, 1982), and phenylephrine (Shur & Checkley, 1982), and that these drugs can potentiate the mydriasis evoked by noradrenaline (Szabadi *et al.*, 1981).

In the present study, we have examined the effects of chronic treatment with ciclazindol and desipramine on pupillary responses to methoxamine (a directly acting α-adrenoceptor stimulant), tyramine (an indirectly acting sympathomimetic amine), and pilocarpine (a directly acting muscarinic receptor stimulant) (see Szabadi *et al.*, 1975, 1980, 1981). The objective of the present study was to contribute to the pharmacological profile of ciclazindol in the autonomic nervous system of human subjects in order to be able to predict possible peripheral side effects and drug interactions. Furthermore, the investigation of the effects of chronic administration rather than of acute single doses (cf. e.g. Ehsanullah *et al.*, 1977) is likely to mimic more faithfully the clinical situation where repeated single doses are administered over the period of several weeks (Ghose *et al.*, 1978).

A preliminary report of some of these results has been presented to the British Pharmacological Society (Kerr & Szabadi, 1979).

Methods

Subjects

Twenty-nine healthy volunteers (22 males and seven females, aged 18 and 30 years) participated in the study. Eighteen subjects were blue-eyed, 10 subjects were hazel-eyed, and one subject was brown-eyed. None of the subjects had any previous history of eye-disease, and no other medication was being taken. All the subjects were informed about the nature and possible risks of the experiment, and all gave written consent. The study was approved by the Ethical Committee of Withington Hospital, Manchester.

Drugs

During Phase II of the experiment (see below), each subject took one of the following medications: ciclazindol hydrochloride (Wyeth Laboratories) 50 mg twice daily, desipramine hydrochloride (Geigy Pharmaceuticals) 50 mg twice daily, or lactose placebo twice daily. The three medications were dispensed in identical capsules for single-blind administration.

Measurement of pupillary responses

Pupil diameter was measured using a photographic technique (Sneddon & Turner, 1969). Each experimental session lasted for 2 h. For the first 15 min the subject was allowed to acclimatise to the lighting conditions in the laboratory. Then three photographs were taken at 5 min intervals to establish the mean resting pupil diameter. This was followed by the instillation of a drop of one of the following solutions into the conjunctival sac of one of the eyes: methoxamine hydrochloride (0.04 M, pH 5.0), tyramine hydrochloride (0.072 M, pH 4.0), or pilocarpine hydrochloride (0.02 M, pH 4.5). The concentrations used were selected on the basis of preliminary experiments showing that these concentrations resulted in reproducible sub-maximal pupillary responses. After the

instillation of the drug solution, the photography of the eyes was repeated every 5 min over a period of 90 min (see Figures 2, 4 and 5). Pupillary responses were calculated as the difference between the mean resting pupil diameter and the diameter of the pupil at maximal dilatation or constriction (mean of last six photographs).

Experimental design

The experiment lasted for 8 weeks during which there were 16 sessions (2 per week, separated by 3 to 4 days) to assess pupillary responses. The 8 weeks of the experiment were divided into three phases: Phase I (2 weeks)—pre-medication control; Phase II (4 weeks)—medication; Phase III (2 weeks)— recovery.

For the analysis of results, data from the first two sessions of Phase I were discarded since the first week of the experiment was regarded as an acclimatization period; the mean of the values obtained in Sessions 3 and 4 was regarded as the pre-treatment control. During Phase II data from Sessions 9 to 12 (3rd and 4th week of medication) were used to calculate the mean pupillary measures for the treatment period, since steady-state plasma levels of the antidepressants had been established by Session 9 (see below, Results). For Phase III, the mean of the measures during Sessions 15 and 16 (final week) was taken as representative of the recovery period.

Plasma levels of antidepressants

In Sessions 5 to 16, a 10 ml sample of blood was taken on each occasion for the assay of ciclazindol or desipramine. The plasma levels of desipramine were assessed by Geigy Pharmaceuticals (Macclesfield) using a double radioisotope derivative method (Carnis *et al.*, 1976), and the levels of ciclazindol were determined by Wyeth Laboratories (Maidenhead) using gas-liquid chromatography.

Results

Resting pupil diameter

The pre-treatment (Phase I) resting pupil diameter (mean ± s.e. mean, $n = 29$) was 5.47 ± 0.14 mm. The effects of the three treatment regimens on resting pupil diameter are shown in Table 1. It is apparent that both ciclazindol and desipramine caused a small but significant increase in resting pupil diameter while placebo had no significant effect. Resting pupil diameter

Table 1 Percentage change from pre-treatment level (mean ± s.e. mean)

	Ciclazindol		*Desipramine*		*Placebo*	
	Phase II	*Phase III*	*Phase II*	*Phase III*	*Phase II*	*Phase III*
Resting pupil diameter	+13.9 ± 2.1*** ($n = 11$)	+3.5 ± 1.9	+8.0 ± 1.6*** ($n = 9$)	−1.4 ± 2.6	−0.8 ± 2.0 ($n = 9$)	−4.3 ± 3.7
Mydriasis evoked by methoxamine	−63.0 ± 7.1*** ($n = 6$)	−20.5 ± 12.0	−79.0 ± 10.1** ($n = 5$)	−49.7 ± 10.5**	+14.3 ±14.8 ($n = 5$)	+7.5 ± 21.5
Mydriasis evoked by tyramine	−17.3 ± 3.8** ($n = 11$)	+1.7 ± 6.7	−25.2 ± 6.8* ($n = 7$)	−5.6 ± 8.4	+16.6 ± 6.7* ($n = 8$)	+11.6 ± 6.3
Miosis evoked by pilocarpine	+36.9 ± 8.7* ($n = 5$)	+16.6 ± 6.6	+39.2 ± 9.1** ($n = 6$)	+10.6 ± 17.7	+4.4 ± 4.0 ($n = 4$)	+11.5 ± 5.9

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (Student's t-test). n = number of subjects studied.

recovered to its original level after the administration of the antidepressants had been discontinued (Phase III).

Mydriasis evoked by methoxamine

The pre-treatment (Phase I) mydriatic response to methoxamine (mean ± s.e. mean, n = 16) was 1.49 ± 0.15 mm. The effects of the three treatment regimens on methoxamine-evoked mydriasis are shown in Table 1. It is apparent that both ciclazindol and desipramine caused a significant antagonism of the response, while placebo had no significant effect. During Phase III there was a considerable decrease in the degree of antagonism by the antidepressants; complete recovery did not occur within 2 weeks after treatment with desipramine had been discontinued. Figure 1 shows examples of individual responses to methoxamine: both ciclazindol and desipramine antagonized the responses. Figure 2 shows how the size of the response to methoxamine changed from session to session in one subject who was treated with desipramine. It is apparent from both Figures 1 and 2 that there was an increase in resting pupil diameter in the presence of the antidepressants.

Mydriasis evoked by tyramine

The pre-treatment (Phase I) mydriatic response to tyramine (mean ± s.e. mean, n = 26) was 2.06 ± 0.11 mm. The effects of the three treatment regimens on the mydriatic response to tyramine are shown in Table 1. It is apparent that both ciclazindol and desipramine caused a significant antagonism of the response to tyramine, while there was a small but statistically

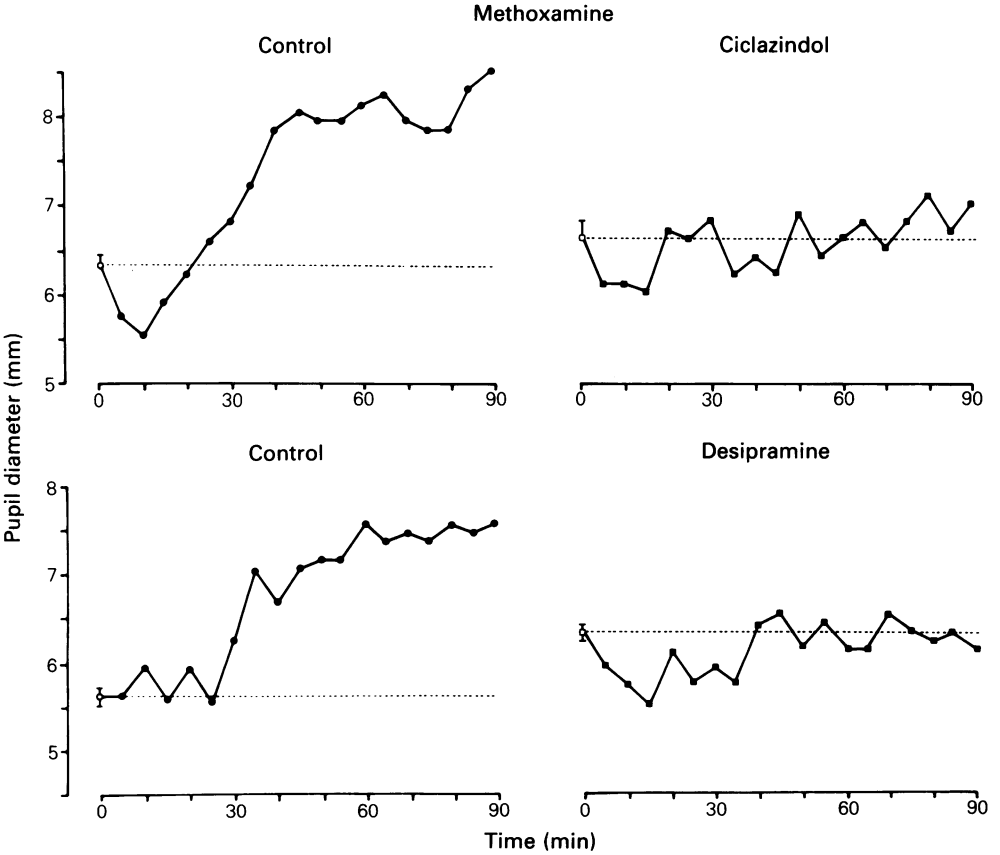

Figure 1 The effects of ciclazindol (top) and desipramine (bottom) on the size of the mydriatic response to methoxamine. The top and bottom recordings were obtained in two different subjects; control: Session 4; ciclazindol or desipramine: Session 12. Ordinate: pupil diameter (mm), abscissa: running time (min) measured from the instillation of the eye-drop (methoxamine hydrochloride, 0.04 M). The open symbols and the vertical bars correspond to the resting pupil diameter (mean ± s.e. mean); the horizontal line indicates the mean resting pupil size; closed symbols correspond to pupil diameter values at 5 min intervals. In the presence of ciclazindol or desipramine the resting pupil diameter increased and the pupil dilatation evoked by methoxamine was antagonized.

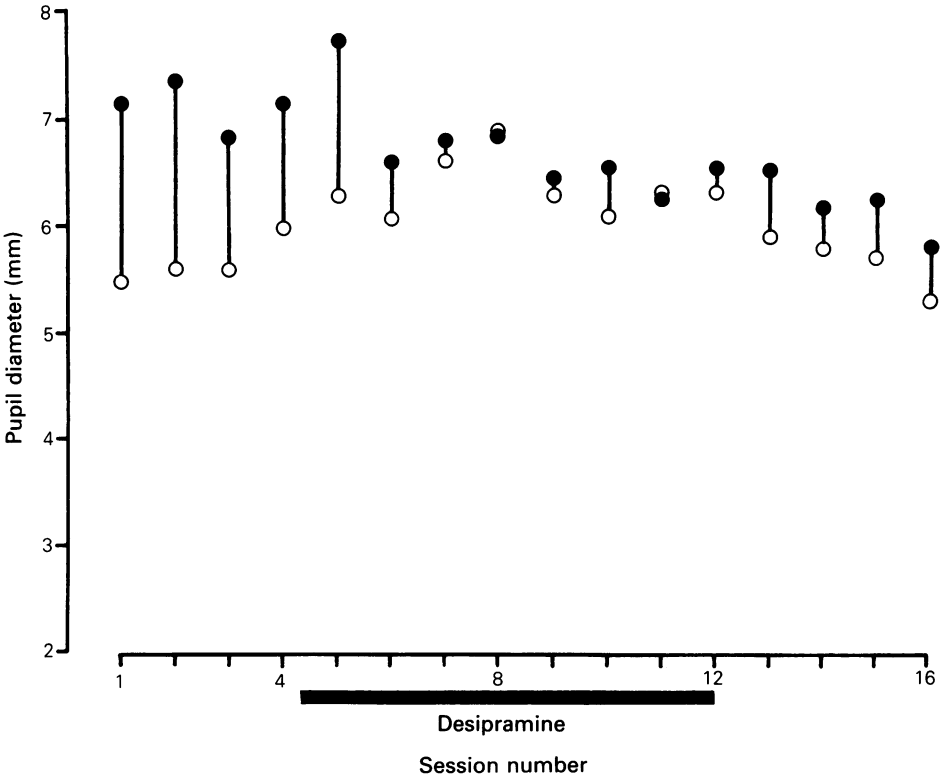

Figure 2 The time-course of change in resting pupil diameter and the size of the mydriatic response to methoxamine in one subject treated with desipramine. Ordinate: pupil diameter (mm); abscissa: running time (sessions). Open circles: resting pupil diameter; closed circles: mean pupil diameter 65–90 min after the instillation of the eye-drop (methoxamine hydrochloride, 0.04 M); vertical bars represent the sizes of the mydriatic responses obtained in individual sessions. Resting pupil diameter increased, and the response to methoxamine was antagonized during the administration of desipramine.

significant increase in the response during the administration of placebo. The responses recovered their original sizes during Phase III.

Miosis evoked by pilocarpine

The pre-treatment (Phase I) miotic response to pilocarpine (mean ± s.e. mean, $n = 15$) was 1.70 ± 0.16 mm. The effects of the three treatment regimens on pilocarpine-evoked miosis are shown in Table 1. It is apparent that ciclazindol and desipramine caused a significant potentiation of the response, while placebo had no significant effect. In Phase III the recovery of the original responses could be observed in the two groups of subjects treated with the antidepressants. Figure 3 shows individual examples of responses to pilocarpine: ciclazindol and desipramine potentiated the responses.

Plasma levels of antidepressants

The mean plasma levels present in Sessions 5–16 are shown in Table 2. It is apparent that steady-state plasma levels were established for both antidepressants during the last 2 weeks of antidepressant treatment (Sessions 9–12). The steady-state plasma level of ciclazindol (μM, mean ± s.e. mean) was 5.90 ± 0.74, and the steady-state plasma level of desipramine (μM, mean ± s.e. mean) was 0.60 ± 0.17. It is apparent from Table 2 that a steady-state level of ciclazindol was established by the first session after the initiation of medication (Session 5), and that the plasma level declined very fast below threshold levels after the discontinuation of the treatment. In the case of desipramine, the build-up of the plasma concentration was gradual, and in fact the steady-state was not

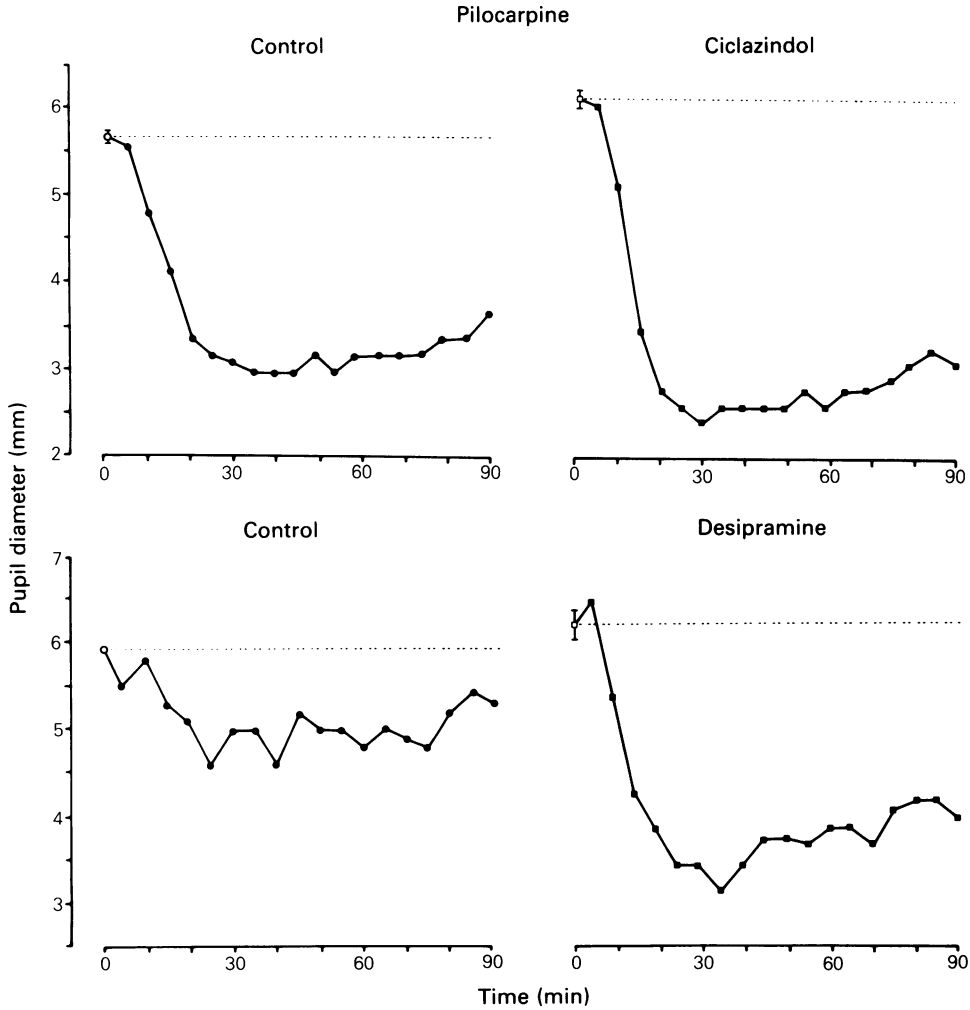

Figure 3 The effects of ciclazindol (top) and desipramine (bottom) on the size of the miotic response to pilocarpine (one drop of pilocarpine hydrochloride, 0.02 M). The top and bottom recordings were obtained in two different subjects. Conventions as in Figure 2. In the presence of ciclazindol or desipramine the resting pupil diameter increased and the pupil constriction evoked by pilocarpine was potentiated.

reached until about 10 days after the initiation of the treatment (Session 8). Similarly, the decline in the plasma level of desipramine following cessation of treatment was slow, and the presence of the drug could be detected even 2 weeks after discontinuation of medication (Session 16).

Discussion

Both ciclazindol and desipramine caused a small (approximately 10%) but significant increase in resting pupil diameter; pupil diameter recovered its original size after the discontinuation of antidepressant medication. The mydriatic effect of desipramine is well-documented in the literature (Szabadi *et al.*, 1980; Shur & Checkley, 1982), and has been attributed to the potentiation of the mydriatic effect of endogenous noradrenaline resulting from the blockade of uptake by the antidepressant (Szabadi *et al.*, 1981). Since ciclazindol, like desipramine, is a potent blocker of noradrenaline uptake (Sugden, 1974), the same mechanism may underly the mydriatic effect of ciclazindol.

Both ciclazindol and desipramine caused a considerable and significant reduction in the size of the mydriatic response to methoxamine. Since the antidepressants also caused an increase

Table 2 Plasma levels of antidepressants, μM (mean ± s.e. mean)

Session number	*Ciclazindol* (n = *11*)	*Desipramine* (n = *9*)
5	5.29 ± 0.75	0.28 ± 0.10
6	5.61 ± 0.72	0.39 ± 0.08
7	6.40 ± 0.87	0.39 ± 0.09
8	4.99 ± 0.44	0.55 ± 0.16
9	6.06 ± 0.84	0.58 ± 0.15
10	5.76 ± 0.61	0.61 ± 0.18
11	5.50 ± 0.61	0.63 ± 0.18
12	6.02 ± 1.49	0.56 ± 0.17
13	0.89 ± 0.67	0.47 ± 0.14
14	ND	0.25 ± 0.09
15	ND	0.19 ± 0.08
16	ND	0.11 ± 0.05

Antidepressant medication was started between Sessions 4 and 5, and terminated between Sessions 12 and 13 (broken line).
ND: not detectable (< 0.59 μM) level of ciclazindol.

in resting pupil diameter (see above), an apparent reduction in the mydriatic response could have resulted from a decrease in the difference between resting pupil size and the size of the maximally dilated pupil. The operation of such a 'ceiling effect', however, could be excluded in the present experiment since the absolute size of the pupil (resting pupil diameter + mydriasis evoked by methoxamine) was less in the presence of the antidepressant than that observed during the pre-treatment phase of the experiment (see Figures 1 and 2). The antagonism of the methoxamine-evoked mydriasis by desipramine is in agreement with earlier reports from this laboratory (Szabadi *et al.*, 1981), and is likely to reflect the blockade of postsynaptic α_1-adrenoceptors since methoxamine is a selective postsynaptic α_1-adrenoceptor stimulant (Langer, 1980). Although ciclazindol has a lower potency than desipramine in blocking post-synaptic α_1-adrenoceptors (Sugden, 1974; Waterfall *et al.*, 1979) the antagonism of the methoxamine-evoked mydriasis by ciclazindol in the present experiment indicates that α_1-adrenoceptor blockade can occur in humans treated with therapeutically recommended doses of the drug. A similar conclusion has been reached by Ghose *et al.* (1978) who found a significant correlation between the plasma concentration of ciclazindol and the reduction in the phenylephrine-evoked pressor response.

Ciclazindol and desipramine antagonized the mydriatic response to tyramine. This observation is in agreement with previous reports of the antagonism of tyramine-evoked mydriasis by amitriptyline (Szabadi *et al.*, 1975) and by desipramine (Shur & Checkley, 1982). Since tyramine is an indirectly acting sympathomimetic amine (Trendelenburg, 1972), the antagonism of the response is likely to reflect the uptake blocking property of the antidepressants; the reduction in the response to tyramine could have been further accentuated by the α_1-adrenoceptor blocking property of these drugs (see above).

Neither ciclazindol nor desipramine showed any antagonism of the miotic response to the muscarinic stimulant pilocarpine, thus confirming earlier observations with desipramine (Szabadi *et al.*, 1980; Shur & Checkley, 1982), and presumably reflecting the low affinity of both desipramine (Snyder & Yamamura, 1977) and ciclazindol (Waterfall *et al.*, 1979) for the muscarinic receptor. An unexpected observation was, however, that the miotic response to pilocarpine was potentiated by both ciclazindol and desipramine. Shur & Checkley (1982) have also reported that the pilocarpine-evoked miosis was potentiated in depressed patients treated with desipramine. The authors attributed this observation to a 'baseline effect': as desipramine increased resting pupil diameter, there was 'greater room for constriction after pilocarpine'. Such an explanation would be appropriate if the pre-treatment (Phase I) responses to pilocarpine were of maximal or supra-maximal size. This, however, was not the case in our experiment: all the pre-treatment responses were submaximal (see Figure 3). Furthermore, it is clear from all the measurements (see, for example, Figure 3) that the absolute size of the pupil (resting pupil diameter minus miotic response to pilocarpine) was smaller in the presence of the antidepressant than before treatment, suggesting a genuine potentiation of the response. (Any change in

the size of the response resulting from the baseline shift could approximate the pretreatment absolute pupil size, but never exceed it; for argument see Szabadi, 1977). There is no immediate explanation for the potentiation. It is noteworthy, however, that no potentiation of the mydriatic response to pilocarpine was reported following single oral doses of desipramine (Szabadi *et al.*, 1980) whereas potentiation was described in the studies involving chronic administration of the drug (present study, and Shur & Checkley, 1982). It is possible, therefore, that the potentiation reflects some long-term adaptive changes in the iris to the presence of the antidepressant.

The twice-weekly assays of the plasma levels of the antidepressants showed that all the subjects complied with the medication throughout the study. There were some major differences between the plasma level profiles of ciclazindol and desipramine (see Table 2): (a) the steady-state plasma level of ciclazindol was attained much faster than that of desipramine; (b) the steady-state plasma level of ciclazindol was approximately ten times as high as that of desipramine; and (c) after discontinuation of treatment, the plasma level declined from steady-state much faster in the case of ciclazindol than in the case of desipramine. The steady-state plasma levels of the two antidepressants obtained in this study are similar to those reported in the literature (for ciclazindol, see Ghose *et al.*, 1978; for desipramine, see Alexanderson, 1972; Rudorfer & Young, 1980). The relatively 'slow' pharmacokinetic profile of desipramine (see also Alexanderson, 1972) could explain the slow recovery from some pharmacodynamic effects of desipramine after discontinuation of treatment: the partial preservation of the antagonism of the mydriatic response to methoxamine during the second week after cessation of treatment was paralleled by the presence of a lower than steady-state concentration of desipramine in the plasma (cf Tables 1 and 2).

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