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Double-Blind Placebo-Controlled Study of the Autonomic Effects of Clovoxamine, Imipramine, and Amitriptyline in Normal Volunteers

William H. Wilson, Jill Rasmussen, Beth Vause, and Gregory Manov

Department of Psychiatry, Duke University Medical Center, Durham, North Carolina (W.H.W.); Kali-Duphar Laboratories, Inc., Columbus, Ohio (J.R., B.V.); Department of Psychiatry, Allen Park VAMC, Allen Park, Michigan (G.M.)

ABSTRACT

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The autonomic effects of clovoxamine, a possible new antidepressant, were compared with placebo, imipramine, and amitriptyline in a double-blind, repeated-measures, latin-square study design, using 16 healthy volunteers. Salivary flow, pupillary response, near-point accommodation, and pilocarpine-evoked miosis were assessed before and 1, 2, and 3 hours after each treatment condition. Dose-related autonomic effects were seen with all three active drugs. Clovoxamine at a 50-mg dose was not distinguishable from placebo. For salivary flow, perhaps the most reliable index of anticholinergic activity, the effects of 100-mg and 150-mg doses of clovoxamine were comparable to those of 50-mg and 75-mg doses of imipramine but were less than those of 50- and 75-mg doses of amitriptyline at 3 hours postdosing.

Key words: anticholinergic, autonomic, antidepressant

INTRODUCTION

The tricyclic antidepressants, of which imipramine and amitriptyline are representative, are widely prescribed for the treatment of depressive disorders. Their clinical use, however, is

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Address reprint requests to William H. Wilson, Dept. of Psychiatry, Duke University Medical Center, Durham, NC.

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complicated by their unwanted effects principally on the autonomic nervous system. Most tricyclic antidepressants cause side effects such as dry mouth, constipation, blurred vision, tachycardia, and urinary retention; these side effects are generally attributed to the anticholinergic properties of the drugs [Blackwell, 1981].

Clovoxamine fumarate is a compound in the series of 2-aminoethyl oximethers of aralkylketones. Preclinical studies showed that clovoxamine had potent noradrenergic and serotonergic reuptake inhibition activity, in common with other known antidepressants, but apparently without the antimuscarinic activity usually associated with these compounds [Claassen and Van der Heyden, 1984].

Early open clinical studies indicated that clovoxamine was an effective antidepressant and was well tolerated [Freeman et al., 1982; Wright et al., 1981; Gelenberg et al., 1985].

In these and later studies, clovoxamine has not been associated with adverse effects on cardiovascular or laboratory test variables. In addition, in contrast with amitriptyline, clovoxamine showed less sedation, greatly reduced anticholinergic effects (as confirmed by salivary flow measurements), and no weight gain [Block and Coleman, 1983]. The pharmacological profile suggested, therefore, that clovoxamine might have specific benefits over other antidepressants.

DESIGN

The autonomic effects of clovoxamine fumarate were studied in healthy volunteers, utilizing a randomized double-blind, placebo-controlled design. Clovoxamine was compared to imipramine and amitriptyline in 16 healthy volunteers using single oral doses of medications administered according to a replicated 8 × 8 latin square. Each of the 16 healthy volunteers was tested at weekly intervals over 8 consecutive weeks. On each occasion, subjects were assessed four times, i.e., baseline and 1, 2, and 3 hours after medication.

DEMOGRAPHIC INFORMATION

Sixteen healthy volunteers between the ages of 18 and 33 years were selected for inclusion. There were eight males (mean age 26.3) and eight females (mean age 24.0 years). All gave informed consent and were paid for their participation.

Physical examinations, electrocardiograms, and laboratory evaluations (hematological and biochemical) were performed before and after the study to insure good physical health. In addition, candidates were excluded if any of the following were present at screening: 1) known hypersensitivity to tricyclic compounds, 2) physical disease requiring concomitant medication, 3) history (past or present) of addiction to alcohol or drugs, 4) habitual use of hallucinogens, 5) known history of psychiatric illness, 6) known history of convulsions or epilepsy, 7) scores outside the normal range on the Hopkins Symptom Checklist, 8) pregnancy or females of childbearing potential not using adequate contraceptive measures.

DRUGS AND DOSAGES

Clovoxamine (50 mg), amitriptyline (25 mg), imipramine (25 mg), and placebo were supplied in indistinguishable grey gelatin capsules for double-blind administration. All drugs were supplied by Duphar B.V., Weesp, The Netherlands.

Each subject received, as single doses, each of the following medications: clovoxamine 50 mg, 100 mg, and 150 mg, amitriptyline 50 mg and 75 mg, imipramine 50 mg and 75 mg, and placebo. The order of medications was randomized in an 8 × 8 latin-square design, one square for males and one square for females. To maintain the double-blind, study drug was

administered as four capsules with one or more placebo capsules given to make up the four. A separate bottle was packaged for each of the eight sessions.

ASSESSMENTS

Screening assessments (presented above) were performed to insure suitability for inclusion. During the study, subjects were assessed at weekly intervals for a total of eight occasions. The measures used to assess the autonomic responses were 1) unstimulated salivary flow [Davies and Gurland, 1961; Blackwell et al., 1978], 2) pupillary diameter [Wilson et al., 1980], 3) pilocarpine-evoked miosis [Szabadi et al., 1980], 4) near-point accommodation [Herxheimer, 1958], and 5) pulse rate and blood pressure (sitting and standing).

SALIVARY FLOW

Weighed containers each holding three dental rolls were used to collect saliva. Each container was labeled for the subject, day, and hour of testing. During testing, a dental roll was placed in each buccal sulcus and one sublingually for 2 minutes. After removal, the three rolls were placed in a sealed, labeled container and reweighed. At each time period (baseline 1, 2, and 3 hours) this procedure was carried out three times with 3-minute rest periods. Average weight gain of the containers over the three trials at each time period was analyzed.

RESTING PUPILLARY DIAMETER

Pupil size was recorded photographically with a Nikon "F" 35-mm camera using a 205-mm close focus lens with a 26-mm Macro adapter. The camera was placed a standard distance (30 cm) from the subject's face, and a consistent light level was maintained over assessment periods. The subject's head was placed against a head rest with the chin in a chin rest so that the position of the eyes and distance from the camera remained constant. Subjects were instructed to relax and to stare at an object placed on the wall in front of them. A small square of paper with a 1.0-cm line on it was taped just below the left eye to serve as a standard for calibration of measurements. Four photographs at 5-minute intervals were made at each time period (baseline, 1, 2, and 3 hours). The pupil size was measured with vernier calipers from the four photographs, and the mean of each four was recorded for analysis.

PILOCARPINE-EVOKED MIOSIS

The pupillary response to pilocarpine was assessed by instilling one drop of pilocarpine hydrochloride (Isopto-Carpine, 0.07 M, pH 4.4) into the conjunctival sac of the left eye and one drop of artificial tear into the conjunctival sac of the right eye. The drops were administered 20 minutes after the 2-hour assessment. The pupils were photographed 40 minutes later, four times at 5-minute intervals, and the mean pupil diameter of the four photographs was calculated. The difference between the diameters of the two pupils was taken as the response to pilocarpine.

NEAR-POINT ACCOMMODATION

The near-point accommodation effect was measured using a test-type moved along a calibrated slide, which was mounted on a stand. For each assessment the subject's forehead was placed against the end of the slide with the positioning held constant for all measurements. Because pilocarpine was administered to the left eye after the 2-hour assessment, only right eye accommodation was measured. All subjects were required to cover the left eye for all

assessments. Two measurements were made with the test-type approaching, and two were made with the test-type receding. The mean of the four measurements was used for analysis. Measurements were made at baseline and 30, 60, 90, 120, 150, and 180 minutes postdosing.

PULSE AND BLOOD PRESSURE

Pulse and blood pressure, sitting and standing, were taken before and 3 hours after administration of study medication. There was a 1.0-minute period between the sitting and standing measurements.

UNWANTED OCCURRENCES

Unwanted occurrences over the 8-week period were recorded for each individual case, and subjects were treated appropriately until the signs/symptom resolved. All signs or symptoms were grouped by preferred terms, using the National Adverse Drug Reaction Dictionary (COSTART) thesaurus [1974].

STATISTICAL METHODS

The study was a repeated (8 × 8) latin-square design. A linear model was fitted to the data. The model included terms for the following main effects: sex, subjects within sex, sessions, and treatment. In addition a term for sex-by-treatment interaction was in the model. This model was fitted to the data collected at each time point.

Tukey's Honestly Significant Difference multiple comparison procedure was applied to all pairwise treatment differences for all time points at the $P < .05$ level [Gill, 1978].

RESULTS

Salivary Flow

The data comparing individual doses of drugs to placebo are presented in Table 1. In comparison with placebo, 50 mg clovoxamine did not decrease salivary flow. All other active treatments showed a reduction in salivary flow, with clovoxamine doses of 150 mg and amitriptyline doses 50 mg and 75 mg reaching a significant difference from placebo at 2 and 3 hours postdosing. Clovoxamine 150 mg and imipramine 75 mg were also significantly different from placebo at 1 hour postdosing.

Interdrug comparisons showed that clovoxamine 150 mg, imipramine 75 mg, and amitriptyline 50 mg and 75 mg all reduced salivary flow in contrast with clovoxamine 50 mg. Additionally, clovoxamine 150 mg was not significantly different from clovoxamine 100 mg, imiprimine 50 mg and 75 mg, or amitriptyline 50 mg and 75 mg at any time period in its effects on salivary flow.

The reduction in salivary flow seen with higher doses of active treatments increased with dosage and was greatest at 2 and 3 hours postdosing. Imipramine 75 mg and amitriptyline 75 mg appeared to have the greatest effect on salivary flow at 3 hours.

A significant sex-by-treatment interaction was noted 3 hours postdosing. This is considered clinically unimportant.

Pupillary Diameter

Results of the analysis of the mean pupillary diameter are presented in Table 2. The analysis of pupillar diameter showed that amitriptyline 75 mg and clovoxamine 150 mg were significantly different from placebo at 3 hours postdosing. Clovoxamine 150 mg produced a

TABLE 1. Mean Salivary Flow

Treatments	Baseline[a] (mean;SD)		Mean change from baseline (mean;SD) 1 hr	2 hr	3 hr
Placebo					
	Mean	1.04	.11	.10	−.06
	SD	.63	.21	.23	.21
Clovoxamine					
50 mg	Mean	.93	.10	−.01	−.08
	SD	.48	.29	.20	.30
100 mg	Mean	1.07	.05	−.22[c]	−.32[b]
	SD	.40	.36	.35	.37
150 mg	Mean	1.03	−.17[c]	−.46[b,c]	−.48[b,c]
	SD	.63	.37	.66	.50
Imipramine					
50 mg	Mean	.84	.05	−.23	−.33[b]
	SD	.37	.21	.23	.24
75 mg	Mean	1.06	−.16[c]	−.52[b,c]	−.58[b,c]
	SD	.46	.30	.38	.39
Amitriptyline					
50 mg	Mean	.91	−.33	−.32[c]	−.42[b,c]
	SD	.44	.25	.22	.30
75 mg	Mean	.92	−.01	−.42[b,c]	−.60[b,c]
	SD	.48	.27	.39	.35

[a]Weight in grams.
[b]Difference from baseline $P \leq .05$.
[c]Difference from placebo at same hour $P \leq .05$.

dilatation of the pupil over time, whereas amitriptyline 75 mg was associated with pupillary constriction.

Interdrug comparisons showed that amitriptyline was significantly different from clovoxamine and imipramine. All pupillary responses were dose related and were maximal at 2 and 3 hours postdosing; doses of clovoxamine and imipramine were associated with pupillary dilatation, whereas doses of amitriptyline were associated with pupillary constriction.

Near-Point Accommodation

There was a statistically significant difference among treatment sessions at baseline for the analysis of near-point accommodation. Baseline mean values for near-point accommodation increased during the first four sessions of the study and then reached a plateau, but this was not due to a carry-over effect of study drug from one session to another. These differences in baseline values were therefore considered to be of no clinical importance. A sex-by-treatment interaction was noted at 1 hour postdosing; however, this was considered to be clinically unimportant.

Because of the large variability among individual treatments in accommodation over sessions, a somewhat different analytic approach was used. Mean responses were determined for each subject on each drug across dose levels (e.g., 50, 100, and 150 mg of clovoxamine), and differences from baseline were determined at 1, 2, and 3 hours. The data for one subject showed large variations over time to all drugs including placebo; therefore, analyses were carried out with and without this subject. Both analyses revealed significant period effects and a drug-by-period interaction. The results of the analyses without this subject are presented in Table 3. Post hoc analyses revealed that for placebo there was no change across time. Compared to placebo all three drugs produced statistically significant increases in near-point

TABLE 2. Mean Pupillary Diameter

Treatments		Baseline[a] (mean;SD)	Mean change from baseline (mean;SD) 1 hr	2 hr	3 hr
Placebo					
	Mean	3.45	−.05	−.06	.15
	SD	0.61	.14	.14	.25
Clovoxamine					
50 mg	Mean	3.51	−.12	.01	.22
	SD	.48	.24	.24	.24
100 mg	Mean	3.50	−.02	.12	.40[b]
	SD	.54	.20	.19	.28
150 mg	Mean	3.44	.05	.17	.52[b,c]
	SD	.52	.25	.28	.31
Imipramine					
50 mg	Mean	3.47	−.09	.04	.15
	SD	.51	.19	.25	.25
75 mg	Mean	3.61	.05	.15	.21
	SD	.95	.44	.33	.45
Amitriptyline					
50 mg	Mean	3.54	−.02	−.10	−.15
	SD	.53	.18	.15	.21
75 mg	Mean	3.51	.04	−.18	−.28[b]
	SD	.57	.19	.28	.38

[a]Baseline values in millimeters.
[b]Difference from baseline $P \leq .05$.
[c]Difference from placebo at same hour $P \leq .05$.

TABLE 3. Near-Point Accommodation

Treatments		Baseline [a] (mean;SD)	Mean change from baseline (mean;SD) 1 hr	2 hr	3 hr
Placebo					
	Mean	117.91	3.21	2.01	7.76
	SD	29.79	9.85	9.21	10.33
Clovoxamine					
	Mean	121.77	5.77	10.34[b]	15.53[b]
	SD	40.19	7.18	15.07	12.04
Imipramine					
	Mean	120.66	2.27	9.80[b]	13.80[b]
	SD	33.33	10.86	10.82	18.02
Amitriptyline					
	Mean	114.96	2.70	17.10[b,c]	22.87[b,c]
	SD	37.38	15.10	18.71	22.32

[a]Baseline values in millimeters.
[b]Difference from baseline $P \leq .05$.
[c]Difference from placebo at same hour $P \leq .05$.

at 2 hours. Amitriptyline had a significantly greater effect than clovoxamine or imipramine. At 3 hours clovoxamine continued to be different from placebo; however, it was not different from imipramine, while amitriptyline had a significantly greater effect than clovoxamine or imipramine.

TABLE 4. Most Frequently Occurring Signs and Symptoms*

		Clovoxamine			Imipramine		Amitriptyline	
Symptom	Placebo	50 mg	100 mg	150 mg	50 mg	75 mg	50 mg	75 mg
Asthenia	3	5	7	12	11	12	9	11
Dry mouth	2	6	4	7	7	5	8	9
Nausea	0	3	5	9	6	4	0	1
Somnolence	3	4	4	5	9	7	10	13
No. reporting no signs/symptoms	3	5	2	0	0	0	0	0
No. reporting at least one sign/symptom	13	11	14	16	16	16	16	16

*No. of subjects reporting symptoms at least once.

Pilocarpine-Evoked Miosis

Following the application of pilocarpine to the left eye, none of the treatments showed a statistically significant difference from placebo. The observed difference in pupil size between the left and right eyes was greatest for clovoxamine 100 mg and 150 mg and least for amitriptyline 75 mg and imipramine 50 mg.

Pulse Rate

The pulse rate (sitting and standing) showed little change for any of the clovoxamine, amitriptyline, or placebo medications. After imipramine 75 mg, the pulse rate showed a maximum mean increase of about 5 beats per minute while sitting and a mean increase of about 7 beats per minute while standing.

Systolic and Diastolic Blood Pressure

No consistent changes in blood pressure were noted after any of the treatments.

Postural Changes in Blood Pressure

No consistent postural changes in blood pressure were noted. Two patients experienced episodes of postural faintness, at amitriptyline 50 mg and 75 mg, respectively. Standing blood pressures were not measured as the subjects felt faint on standing.

Safety Assessments

Physical examinations, electrocardiograms, and laboratory tests were performed before and after a subject's participation in the study. No clinically important changes from baseline were noted in any individual.

Concurrent Signs and Symptoms

The most frequently reported symptoms during the study included asthenia, dry mouth, nausea, and somnolence. Presented in Table 4 is a summary of the number of reports for each drug and placebo. Analysis of the numbers of reports relative to placebo suggest the following: 1) somnolence—reported more frequently with imipramine and amitriptyline; 2) asthenia—reported more frequently with imipramine, amitriptyline, and clovoxamine 150 mg; 3) dry mouth—reported by all treatments with the highest frequency after amitriptyline; 4) nausea—reported more frequently on clovoxamine and imipramine with a higher frequency on clovoxamine 150 mg. Placebo had the lowest incidence of reports of all the treatments.

DISCUSSION

This study was designed to examine the autonomic effects of clovoxamine relative to amitriptyline, imipramine, and placebo. The measures used to assess anticholinergic activity were salivary flow, pupillary diameter, pilocarpine-evoked miosis and near-point accommodation. Of these four measures, three yielded statistically significantly results, which were consistent with the well-documented antimuscarinic properties of antidepressants [Blackwell, 1981; Soloman et al., 1977]. Pulse and blood pressure were also used to compare the autonomic effects of the study drugs.

Salivary flow has been established as an accurate and reproducible index of anticholinergic activity and appeared from this study to be a sensitive measure of anticholinergic effects. No reduction in salivary flow occurred with 50 mg clovoxamine, whereas with all other treatments a dose-related reduction in salivary flow was seen. Amitriptyline 75 mg appeared to have the greatest effect on salivary flow.

With respect to pupillary diameter, the anticipated anticholinergic effect is mydriasis. The results of this study confirmed the findings of the animal studies that clovoxamine had a tendency to cause pupillary dilation [Claassen and Van der Heyden, 1984]. Imipramine was also seen to be weakly mydriatic. In contrast, both doses of amitriptyline induced miosis. This paradox has been reported by other investigators [Wilson et al., 1983; Kopera, 1978; Peck et al., 1979]. The explanation for this effect on resting pupil diameter may be in the combined effect of the drug on both cholinergic and adrenergic mechanisms. The mydriasis resulting from the blockade of muscarinic receptors will be opposed by the miosis resulting from the stronger blockade of alpha-adrenergic receptors [Szabadi et al., 1980]. There is also evidence that there may be serotonergic fibers, which innervate the eye and may participate in the regulation of pupil diameter.

In order to increase the specificity of the anticholinergic tests, one can measure not only changes in baseline functions such as pupil diameter but also tissue responses to exogenously administered selective cholinoceptor stimulants, e.g., pilocarpine-evoked miosis. In the present study, the changes seen in responses to pilocarpine, although not statistically significant, are consistent with the findings of other studies [Blackwell, 1981].

With respect to near-point accommodation, the variation in baseline responses, both within each patient and within each session, made interpretation of the results difficult. Factors such as subjective feelings of the participants, "learning effect," variations in environment, and observer error could have an influence on the results. Nonetheless the mean effects (averaged across dose) for each drug were consistent with the other measures, indicating a stronger effect of amitriptyline and similar levels of effects for clovoxamine and imipramine.

Another major area of concern with the tricylic compounds since their introduction is their toxic effects on the cardiovascular system, both in usually prescribed dose ranges and in overdose [Blackwell, 1981]. The effects that are commonly seen in usual dose ranges include increase in pulse rate and postural hypotension. In the study, the episodes of faintness seen with amitriptyline and the increase in pulse rate seen with imipramine are consistent with the drug profiles.

Clovoxamine's lack of any effects on cardiovascular variables, particularly with regard to postural changes in arterial blood pressure and pulse rate, confirm the findings of earlier studies.

The nausea seen with clovoxamine in this study is consistent with the findings of previous studies. Fewer reports of somnolence were seen after administration of clovoxamine in contrast with amitriptyline and imipramine. While this is unlikely to be due to central anticholinergic activity, a lower incidence of somnolence could be a useful characteristic of clovoxamine, particularly where there is potential for an interaction with other drugs or alcohol [Wilson and Ban, 1986].

CONCLUSIONS

Dose-related autonomic effects are seen following the administration of single doses of clovoxamine, imipramine, and amitriptyline in healthy volunteers.

The autonomic effects of single doses of clovoxamine 50 mg are indistinguishable from placebo, while 50-mg doses of imipramine and amitriptyline produced significant effects. The results suggest that on a milligram-to-milligram basis the autonomic effects of clovoxamine would appear to be less than for amitriptyline, but more comparable to imipramine.

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