Br. J. clin. Pharmac. (1983), **15**, 385S–392S

A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY TO COMPARE THE AUTONOMIC EFFECTS OF FLUVOXAMINE WITH THOSE OF AMITRIPTYLINE AND DOXEPIN IN HEALTHY VOLUNTEERS

W.H. WILSON, H. HIGANO, Y. PAPADATOS, S. KELWALA & T.A. BAN

Vanderbilt University Department of Psychiatry and Tennessee Neuropsychiatric Institute, 1501 Murfreesboro Road, Nashville, TN 37217, USA

1 A double-blind placebo- and standard-controlled study was designed to determine the autonomic effects of fluvoxamine, a putative antidepressant possessing a high 5-hydroxytryptamine (5-HT) re-uptake-blocking activity with essentially no effects on noradrenaline. The study employed single doses of fluvoxamine (50 mg, 75 mg and 100 mg), amitriptyline (50 mg and 75 mg), doxepin (50 mg and 75 mg) and placebo, each of which was administered to 17 healthy volunteers according to a repeated-measures latin square design balanced for drug carry-over.

2 Both amitriptyline (Ami) and doxepin (Dox) produced statistically significant decreases in salivary flow relative to placebo, and these effects were still present 24 h after taking medication. For none of the doses of fluvoxamine (Flu) tested did the differences from placebo (Plac) approach significance. There were no differences between the mean response to Ami and Dox, and equivalent dose levels produced similar profiles of differences from Plac.

3 Both Ami and Dox produced significant decreases in pupil diameter relative to Plac. Corresponding doses of Ami and Dox produce remarkably similar effects on pupil diameter and the differences from Plac in mean responses were virtually identical. There was a suggestion that higher doses of Flu (75 mg and 100 mg) may produce increases in pupil diameter; however, the effect was not present unless adjustments (covariance analysis) were made for baseline values, and the mean response over the three doses was not different from Plac.

4 Although there was a tendency toward reduced palpebral fissure size, with the effects of Ami and Dox being greater than Flu, there were no reliable, significant differences in this measure.

5 Fluvoxamine neither produced significant changes in pulse rate, systolic and diastolic blood pressure or mean arterial pressure, nor were there effects in those parameters as a function of postural change. In contrast, Dox produced decreases in systolic and diastolic blood pressures. Neither Ami nor Dox produced significant effects on systolic, diastolic or mean arterial blood pressure related to postural change, but three subjects complained of symptoms compatible with orthostatic hypotension after Dox 75 mg.

Introduction

Animal pharmacology studies have shown that most of the presently available antidepressants have central and peripheral anticholinergic activity that may lead to unwanted clinical effects (Snyder & Yamamura, 1977; Blackwell, 1981). In humans these atropine-like effects include the peripheral symptoms of dry mouth, altered cardiac rate, urinary retention and exacerbation of glaucoma. Central anticholinergic effects include delirium, hyperpyrexia, stupor and coma. These symptoms may be particularly severe in middle aged and geriatric patients, who represent the majority of those treated with antidepressants. In addition, since it has been demonstrated that many of the peripheral symptoms are associated with the illness (Mathew *et al.*, 1979, 1980), treatment with antidepressants that have significant anticholinergic effects may aggravate these symptoms.

Fluvoxamine is a non-tricyclic compound in the series of 2-amino-ethyloximethers of the aralkyl ketones. It possesses a high 5-hydroxytryptamine (5-HT) re-uptake inhibiting activity with negligible, if any, effect upon noradrenaline re-uptake (Claassen *et al.*, 1977). In contrast to the tricyclic antidepressants, animal pharmacology studies suggest that fluvoxamine may be characterized by a low incidence of anticholinergic activity. To evaluate the autonomic

0264-3334/83/0400-3850$02.00

activity of fluvoxamine, a double-blind, placebo- and standard- (Ami and Dox) controlled study was performed with healthy volunteers.

Methods

Design

The study employed repeated single doses of the study drugs and placebo administered according to a latin square design that was balanced for drug carry-over effects. Each subject was tested at weekly intervals for a total of 8 assessment days. On each day the assessments were repeated five times, i.e., baseline and 1, 2, 3 and 24 h post-medication.

Treatments

Each of the subjects received in the order prescribed by the latin square each of the following:

fluvoxamine 50 mg, 75 mg and 100 mg (Flu 50, Flu 75, Flu 100)
amitryptyline 50 mg and 75 mg (Ami 50 and Ami 75)
doxepin 50 mg and 75 mg (Dox 50 and Dox 75)
placebo (Plac)

For each of the three active drugs, the dose was in the form of 25 mg capsules; therefore, to provide for double-blind administration, medication for each day was given as four capsules. On all days, except when the 100 mg dosage of fluvoxamine was administered, one or more of the four capsules contained placebo. Medication was administered with water.

Subjects

A total of 17 healthy volunteers, eight males and nine females, participated in the study. One additional female was entered into the study to compensate for a loss of data due to an equipment malfunction.

The ages ranged from 18 to 34 years with a mean of 25.3 years. All subjects were given a physical examination, including ECG and laboratory tests, before entering the study and at the end of their participation. Written informed consent was obtained from each after the nature of the drugs and the purpose of the study had been explained. The subjects were paid for their participation.

Assessments

Assessment of pupillary diameter (PD), palpebral fissure size (PFS) and salivary flow (SF) were made immediately before and 1, 2, 3 and 24 h after taking medication. Pupil size was recorded photographically with a 35-mm camera and a 205-mm close focus lens with a 26-mm Macro ring adaptor. The end of the lens was placed 30 cm from the subject's face. 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 were held constant. All assessments were made in a room with outside light eliminated. In addition, light level was measured to assure consistency. A small square of paper with a 1.0 cm line drawn on it was taped just below the left eye to serve as a standard for measurement calibrations. During assessments, the subject was instructed to relax and stare at a point marked on the camera above the lens. Four photographs on high speed colour slide (ASA-400) film were made at each of the assessment periods (Wilson *et al.*, 1980).

To record pupil size from the developed film, the slide was placed in a projector, and the image was set so that the 1.0-cm standard measured precisely 1.0 cm. Measurements were made with vernier calipers from the four pictures at each time interval, and the mean of each four was recorded for analysis. Palpebral fissure size was measured from these same photographs, again with the mean of the four at each interval being recorded for analysis.

Salivary flow measurements followed procedures developed by Davis & Gurland (1961) and Blackwell *et al.* (1978). For each assessment period, three plastic sealable containers were prepacked with three dental rolls, labelled and weighed. During assessments, one dental roll was placed in each buccal sulcus and one sublingually. These rolls remained in place for 2 min, then were removed and resealed in the container. The procedure was repeated three times at each assessment period with a 3 min rest between each assessment. The mean change in weight at each assessment period was recorded for analysis. During each 3 min rest in SF measurements, two of the four photographs for PD and PFS were taken. Thus, the entire assessment period required 12 min.

In addition to the above measures, sitting and standing blood pressure and pulse rate were recorded at 0, 3 and 24 h. At each time the subjects were required to sit for 10 min before assessments were taken, and standing values were taken 1 min after rising.

All subjects were required not to eat within 2 h of beginning each assessment day and not to consume alcohol within 24 h of the session. If at all possible, assessments were conducted at the same time of day, between 12.00 and 17.00 h on each assessment day. Upon the subject's arrival at the testing centre, they were required to rest for 10 min before beginning. Following baseline blood pressure and pulse rate measures, baseline PD, PFS and SF measures were taken and then medications were administered. Subjects were required to wait in a sitting room between assessments, where they could read or work.

Data analysis

Analyses of variance and covariance (via linear regression) were calculated on all dependent variables at each post-medication time (i.e., 1, 2, 3 and 24 h). For each dependent variable, an overall analysis was performed which was followed by individual contrast of all doses of drugs against placebo. Individual contrast among the mean responses to the three active agents and placebo were also performed after the mean responses had been determined by averaging over dose levels for each drug, i.e., the mean response for each subject to each drug was determined by averaging his/her responses over the dose levels of the drug at each time period. These mean responses were then compared at each time period by employing the analysis of variance model described above. The following discussion of results that pertain to these 'mean' effects (i.e., averaged across dose levels) will employ the abbreviations Flu, Ami and Dox without reference to dose level.

Results

Study population

Fifteen of the 17 subjects, eight males and seven females, completed the entire study. Two females were withdrawn because they found the sedation effects experienced with some doses to be intolerable.

Salivary flow

An initial analysis revealed there were no differences at baseline (before drug) between the eight treatments and no differences between males and females. The results of sequential analyses of variance, which compared the individual treatments to placebo, are depicted in Figure 1. Plotted in this figure are the mean differences from Plac in grams of saliva for each of seven contrasts. In these contrasts the response to Plac is subtracted from the response to the specific drug. At 1 h post-medication none of the treatment effects was significantly different from placebo. By 2 h, Ami 50, Ami 75, Dox 50 and Dox 75 had produced significant decreases in salivary flow; effects which were increased further at 3 h. Salivary flow continued to be significantly reduced at 24 h for Ami 75 and Dox 50 and Dox 75 (and nearly significant for Ami 50, $P = 0.057$). At no point were Flu 50, 75 or 100 different from placebo.

To allow comparison among Flu, Ami, Dox and Plac, the mean responses (average over the respective doses) were calculated. Presented in Table 1 are the results of these analyses. Relative to Plac, the result for mean responses is essentially the same as for the individual dosage results. In addition, at 1 h

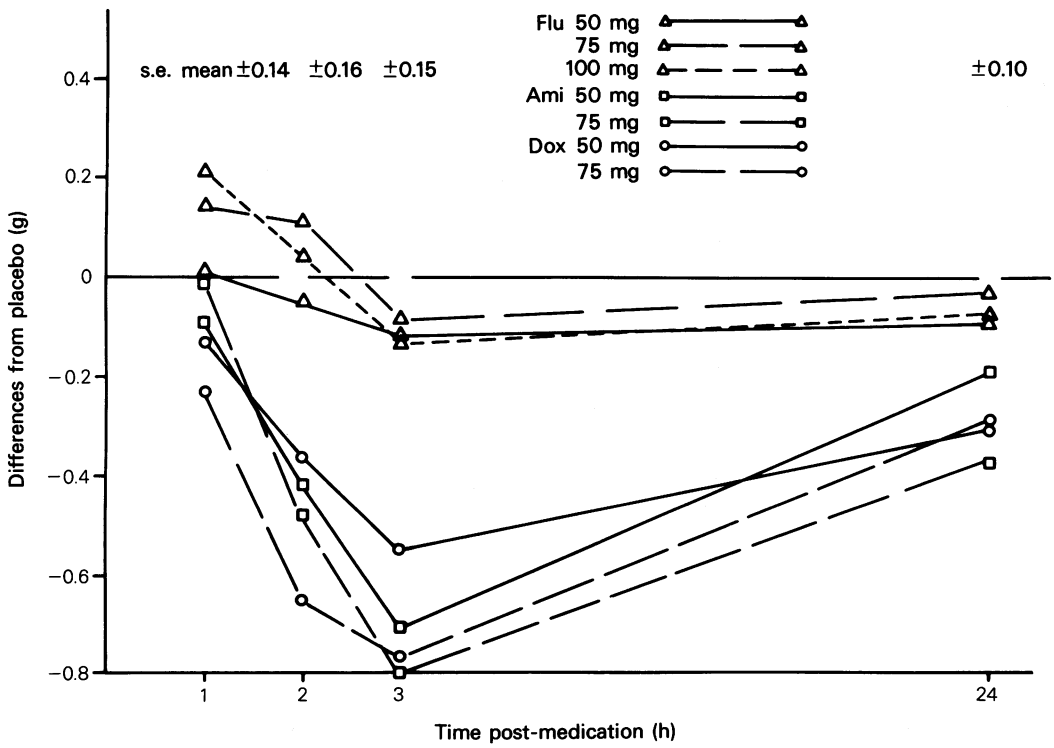

Figure 1 Mean salivary flow—individual dose effects.

post-medication, salivary flow was significantly lower following Dox than following Flu. At 2, 3 and 24 h for both Ami and Dox salivary flow was significantly lower than for Flu. At no time was there a difference between Ami and Dox; the effects being very similar in magnitude.

Pupil diameter

No differences at baseline (pre-drug) were found between the eight treatments, nor were there differences between males and females. The results of sequential analyses of variance, which compared the effects of individual doses of the active drug to placebo, are presented in Figure 2. Plotted in this figure are the mean differences (in mm), for each of the seven contrasts. At none of the four periods (1, 2, 3 or 24 h) did any of the three doses of Flu differ from Plac. When baseline values were covaried from each analysis, there was a suggestion that Flu (75 and 100 mg) produced increases in pupil diameter. However, these differences were not consistent across doses nor assessment periods.

In contrast to the expected anticholinergic effects, both Ami 75 and Dox 75 produced significant decreases (miosis) in pupil diameter relative to Plac, and these effects were present at 2, 3 and 24 h post-drug.

Comparisons among the mean responses for each assessment showed that both Ami and Dox produced significant decreases in pupil diameter, relative to Flu and Plac, at 2 and 3 h post-drug. For Dox the difference from Flu was still significantly different at 24 h (Table 2). There were no significant differences between Ami and Dox, neither were there significant differences between Flu and Plac.

Palpebral fissure

No overall statistical differences suggesting treatment effects were revealed by analysis of variance, and although analysis of covariance indicated differences at 1 and 2 h post-drug, these were not consistent for both males and females. There was, however, a trend suggesting a decrease in palpebral fissure openings for Flu, Ami and Dox as is indicated by the mean responses averaged over the respective doses of each drug.

Pulse rate

There were no statistically significant effects on sitting pulse rate, when the mean response for each drug was compared to Plac at 3 and 24 h post-drug. Neither were there differences in standing pulse rate when compared to Plac. However, there was a tendency for Flu to decrease standing pulse rate relative to Plac, while Ami and Dox tended to increase it; thus, there were significant differences in pulse rate between Flu and both Ami and Dox at 3 and 24 h (Table 3). There were also significant differences between Flu and both Ami and Dox in postural change

Table 2 Mean differences in pupil diameter for each contrast

	Time after dosing (h)			
Contrast†	*1*	*2*	*3*	*24*
Flu–Plac	0.00	−0.05	0.05	0.01
Ami–Plac	−0.18	−0.42***	−0.50**	−0.23
Dox–Plac	−0.18	−0.42***	−0.47**	−0.29
Flu–Ami	0.18	0.37***	0.55***	0.23
Flu–Dox	0.18	0.37***	0.52***	0.28*
Ami–Dox	−0.01	0.00	−0.03	0.06
Plac mean (mm)	4.45	4.68	4.73	4.62

* $P = \leq 0.05$; ** $P = \leq 0.01$; *** $P = \leq 0.001$.
† Contrast determined by subtracting means in the direction indicated. Mean responses determined by averaging over doses of each drug before contrasts were calculated.

Table 1 Mean differences in salivary flow for each contrast

	Time after dosing (h)			
Contrast†	*1*	*2*	*3*	*24*
Flu–Plac	0.120	0.034	−0.111	−0.067
Ami–Plac	−0.039	−0.448**	−0.760**	−0.279**
Dox–Plac	−0.181	−0.504**	−0.659**	−0.298**
Flu–Ami	0.159	0.482**	0.649**	0.211*
Flu–Dox	0.301**	0.538**	0.548**	0.231**
Ami–Dox	0.142	0.056	−0.101	0.019
Plac mean (g)	1.294	1.256	1.356	1.157

* $P = \leq 0.01$; ** $P = \leq 0.001$
† Contrast determined by subtracting means in the direction indicated. Mean responses determined by averaging over doses of each drug before contrasts were calculated.

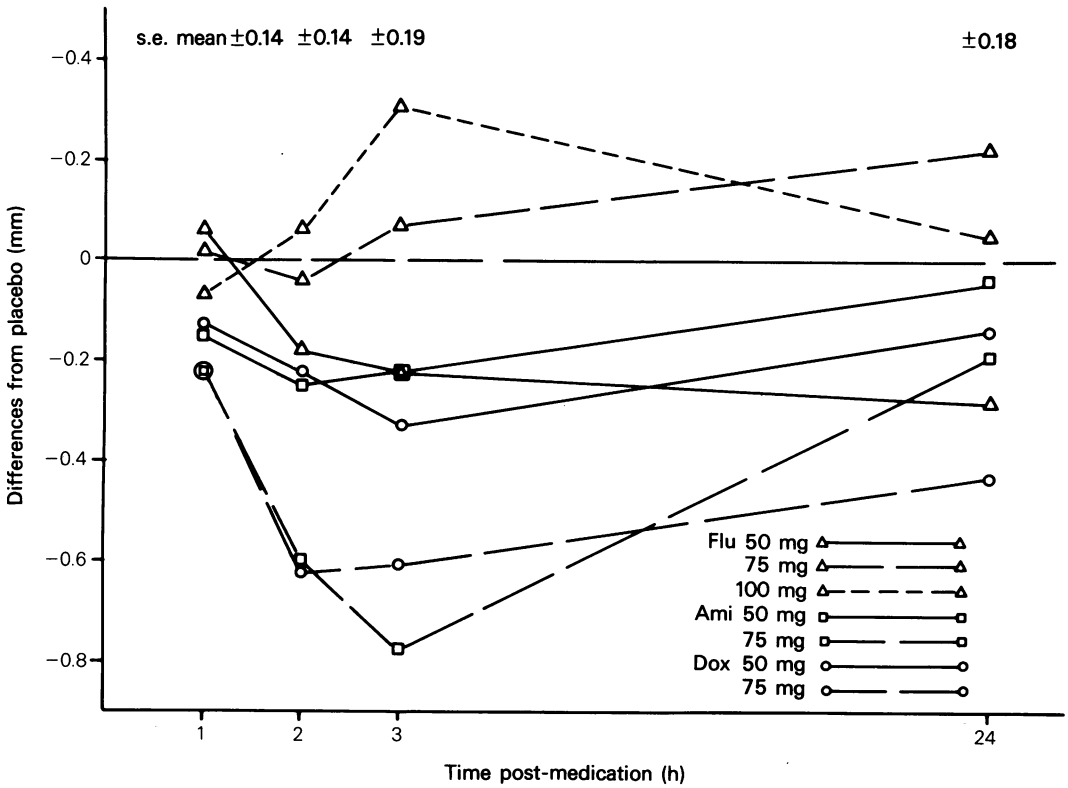

Figure 2 Mean pupil diameter—individual dose effects.

of pulse rates. Both Ami and Dox tended to increase pulse rate more on standing relative to Plac, but only Ami produced a significant postural change in pulse rate relative to Plac.

Blood pressure

As indicated in Table 3, Dox tended to produce changes in sitting and standing systolic and diastolic blood pressure when compared to Plac as well as compared to Flu and Ami. Neither Flu or Ami produced significant changes relative to Plac, and none of the drugs produced statistically significant effects on postural changes in systolic or diastolic blood pressure. However, with Dox 75, three subjects reported dizziness on standing at 3 h post-drug, suggestive of orthostatic hypotension. Analyses of variance at 24 h indicated no significant effects on blood pressure.

Mean arterial pressure (MAP) was calculated for sitting, standing and postural change on the basis of the following equation:

$$\text{MAP} = \frac{\text{Systolic BP} + 2\,\text{Diastolic BP}}{3}$$

Analyses of sitting and standing values at 3 h revealed that Dox significantly reduced MAP (sitting and standing) relative to Plac, while neither Flu nor Ami were different from Plac (Table 3). Although not statistically significant, both Ami and Dox produced greater decreases in MAP postural change relative to Plac than were present for Flu. These effects on MAP (sitting, standing and postural) were no longer present at 24 h post-drug.

Subjective reports

Subjects' reports of sedation were recorded as were investigator observations of 'sleepiness' and/or 'sleeping' between assessments. Flu, Ami and Dox produced increases in the mean number of reports at 2 and 3 h post-drug (Table 4).

Discussion

The findings for amitriptyline and doxepin on the salivary flow measure are consistent with those reported by numerous investigators (Ghose *et al.*, 1976; Blackwell *et al.*, 1978; Kopera, 1978; Peterson *et al.*,

Table 3 Mean difference in pulse rate (beats/min) and blood pressure (mm Hg) for each contrast at 3 and 24 h after dosing

Contrast	*Pulse rate 3 h* Sitting	Standing	Change[a]	*Pulse rate 24 h* Sitting	Standing	Change
Flu–Plac[b]	–0.6	–3.5	–2.9	–2.9	–4.8	1.9
Ami–Plac	–0.8	4.2	–4.9*	–0.5	2.2	–2.6
Dox–Plac	0.6	4.7	–4.1	0.2	1.4	–1.2
Mean Plac	67.6	80.1		74.6	87.8	
	Systolic blood pressure 3 h Sitting	Standing	Change[a]	*Systolic blood pressure 24 h* Sitting	Standing	Change
Flu–Plac	2.6	3.3	–0.7	1.4	0.9	–0.7
Ami–Plac	1.3	–0.5	1.7	–1.0	–1.1	0.1
Dox–Plac	–6.7*	–9.4*	2.7	–2.9	–2.2	–0.7
Mean Plac (mm Hg)	101.6	99.3		104.2	100.8	
	Diastolic blood pressure 3 h Sitting	Standing	Change[a]	*Diastolic blood pressure 24 h* Sitting	Standing	Change
Flu–Plac	–0.7	–0.3	–0.4	3.1*	0.8	2.3
Ami–Plac	1.0	–0.8	1.7	1.9	0.8	1.0
Dox–Plac	–3.1*	–4.5*	1.4	0.5	–0.3	0.8
Mean Plac (mm Hg)	67.9	70.8		63.8	67.8	
	Mean arterial pressure[c] 3 h Sitting	Standing	Change[a]	*Mean arterial pressure 24 h* Sitting	Standing	Change
Flu–Plac	0.4	0.8	–0.4	2.0	0.8	1.2
Ami–Plac	1.0	–0.8	1.8	0.9	0.2	0.7
Dox–Plac	–4.4*	–6.2*	1.8	–0.7	–0.9	0.2
Mean Plac (mm Hg)	74.2	80.4		77.2	78.8	

* $P = \leq 0.05$
[a] Postural change = Sitting – Standing.
[b] Mean response determined by averaging over doses of each drug before contrasts were calculated.
[c] Mean arterial pressure = (Systolic BP + 2 Diastolic BP)/3.

Table 4 Number of reports of somnolence

Time after dosing (h)	*Plac*	*Flu*†	*Ami*†	*Dox*†
1	1	2.0	4.0	4.5
2	1	4.7	10.0***	11.5***
3	1	4.7	11.5***	13.0***
24	0	0.3	2.5*	2.0

* $P = \leq 0.05$; *** $P = \leq 0.001$
† Number of reports for Flu, Ami and Dox represent means determined across dose levels for each drug.

1978; Arnold *et al.*, 1981). The finding that they produce essentially the same level of effects for equivalent doses, although inconsistent with expected effects based upon reported differences in their potency in binding to muscarinic acetylcholine receptors (Snyder & Yamamura, 1977) is not inconsistent with reports using the same methodology of assessing salivary flow (Arnold *et al.*, 1981). The reliability of the findings for amitriptyline and doxepin would appear to lend credence to the proposal that fluvoxamine has little, if any, anticholinergic effect.

Generally accepted information on the innervation of the iris indicates that there are both α-adrenergic (radial muscle-contraction-mydriasis) and muscarinic-cholinergic (sphincter muscle-contraction-miosis) receptors, with the cholinergic effect being more potent (Mayer, 1980). The anticipated anti-cholinergic effect would be mydriasis. However, both amitriptyline and doxepin produced significant

miotic changes, and these changes were very similar for equivalent doses. Other investigators have reported similar miotic changes following amitriptyline (Kopera, 1978; Peck *et al.*, 1979), and there are indications that it is the α-receptor-adrenergic antagonism that causes miosis and even Horner's syndrome (Jones, 1959; Szabadi *et al.*, 1975; Kerr & Szabadi, 1979). However, there are also reports that no change in resting pupil size are observed with amitriptyline which attest to the complex nature of the interaction between cholinergic and adrenergic mechanisms in the regulation of pupil size (Szabadi *et al.*, 1980; Shur & Checkley, 1982).

In contrast to amitriptyline and doxepin, there was some indication that fluvoxamine in higher doses may produce an increase in pupil size, although overall there was no significant difference from placebo. Because the findings with salivary flow would indicate that fluvoxamine has virtually no effect on muscarinic receptors, these opposite findings suggest other mechanisms may be involved in the regulation of pupil size, and indeed there is evidence that there may be 5-hydroxytryptaminergic fibres that innervate the eye and may co-participate in the regulation of pupil diameter (Moro *et al.*, 1981).

The methodology employed for recording pupil size differs from others in the use of a 1.0 cm standard taped just under the eye. It was our observation that, even with the subjects being placed in as nearly constant conditions as possible, there would still be fluctuations in the projected size of the standard, thus also the pupil, requiring readjustment of the projected image before measurements were taken. Considering the very minimal changes that took place in pupil size, the standard served to correct for variability that might otherwise have obscured the effects. Such variability may partially explain the conflicting findings regarding the effects of amitriptyline on pupil size.

Results of the cardiovascular measures are consistent with the expected effects of both amitriptyline and doxepin (Arnold *et al.*, 1981). Amitriptyline and doxepin both tended to increase pulse rate, leading to significant differences between fluvoxamine and each of the other drugs; however, none of the drugs was significantly different from placebo. Although doxepin had the most pronounced effects on systolic and diastolic blood pressure as well as mean arterial pressure, the observation that three subjects experienced symptoms compatible with orthostatic hypotension while receiving Dox 75 was not supported by statistically significant postural changes in either mean arterial, systolic or diastolic readings in the total sample.

In summary, it would appear that the proposal that fluvoxamine does not possess significant anticholinergic effects is supported by the findings of this study. Certainly all three drugs produced different patterns of effects on the measures. The use of a calibration standard in pupil measurements would appear to enhance the sensitivity of this index of autonomic activity.

References

ARNOLD, S.E., KAHN, R.J., FALDETTA, L.L., LAING, R.A. & McNAIR, D.M. (1981). Tricyclic antidepressants and peripheral anticholinergic activity. *Psychopharmacology*, **74**, 325–328.

BLACKWELL, B. (1981). Adverse effects of antidepressant drugs. Part 1: Monoamine oxidase inhibitors and tricyclics. *Drugs*, **21**, 201–219.

BLACKWELL, B., STEFOPOULOS, A., ENDERS, P., KUZMA, R. & ADOLPHE, A. (1978). Anticholinergic activity of two tricyclic antidepressants. *Am. J. Psychiat.*, **135**, 722–730.

CLAASSEN, V., DAVIES, J.E., HERTTING, G. & PLACHETA, P. (1977). Fluvoxamine, a specific 5-hydroxytryptamine inhibitor. *Br. J. Pharmac.*, **60**, 505–516.

DAVIS, B.M. & GURLAND, J.B. (1961). Salivary secretion in depressive illness. *J. psychosom. Res.*, **5**, 269–275.

GHOSE, K., COPPEN, A. & TURNER, P. (1976). Autonomic actions and interactions of mianserin hydrochloride (Org. GB 94) and amitriptyline in patients with depressive illness. *Psychopharmacology*, **49**, 201–204.

JONES, S. (1959). Miosis following administration of chlorpromazine and related agents. *Am. J. Psychiat.*, **115**, 817–818.

KERR, F.A. & SZABADI, E. (1979). Interaction of desimipramine and ciclazindol with adrenergic mechanisms in the human iris. *Br. J. clin. Pharmac.*, **8**, 396P–397P.

KOPERA, H. (1978). Anticholinergic and blood pressure effects of mianserin, amitriptyline and placebo. *Br. J. clin. Pharmac.*, **5**, 29S–34S.

MATHEW, R.J., WEINMAN, M. & CLAGHORN, J.L. (1979). Xerostomia and sialorrhea in depression. *Am. J. Psychiat.*, **136**, 1476–1477.

MATHEW, R.J., WEINMAN, M. & CLAGHORN, J.L. (1980). Tricyclic side effects without tricyclics in depression. *Psychopharmac. Bull.*, **16**, 58–60.

MAYER, S.E. (1980). Neurohumoral transmission and the autonomic nervous system. In *The Pharmacological Basis of Therapeutics*, (6th edn), eds Goodman, A. & Gilman, L., pp. 56–90, New York: MacMillan Publishing Co. Inc.

MORO, F., SCAPAGNINI, U., SCALETTA, S. & DRAGO, F. (1981). Serotonin nerve endings and regulation of pupillary diameter. *Ann. Ophthalmol.*, April, 487–490.

PECK, A.W., BYE, C.E., CLUBLEY, M., HENSON, T. & RIDDINGTON, C. (1979). A comparison of bupropion hydrochloride with dexamphetamine and amitriptyline in healthy subjects. *Br. J. clin. Pharmac.*, **7**, 469–478.

PETERSON, G.E., BLACKWELL, B., HOSTETLER, R.M., KUZMA, R. & ADOLPHE, A. (1978). Anticholinergic activity of the tricyclic antidepressants desipramine and doxepin in non-depressed volunteers. *Commun. Psychopharmac.*, **2**, 145–150.

SHUR, E. & CHECKLEY, S. (1982). Pupil studies in depressed patients: An investigation of the mechanism of action of desipramine. *Br. J. Psychiat.*, **140**, 181–184.

SNYDER, S.H. & YAMAMURA, H.J. (1977). Antidepressants and the muscarinic acetylcholine receptor. *Arch. gen. Psychiat.*, **34**, 236–239.

SZABADI, E., GASZNER, P. & BRADSHAW, G.M. (1980). The peripheral anticholinergic activity of tricyclic antidepressants: Comparison of amitriptyline and desipramine in human volunteers. *Br. J. Psychiat.*, **137**, 433–439.

WILSON, W.H., PETRIE, W.M. & BAN, T.A. (1980). Possible lack of anticholinergic effects with mianserin: A pilot study. *J. clin. Psychiat.*, **40**, 63–65.