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Cardiovascular (ECG and systolic time intervals) and anticholinergic effects of repeated doses of femoxetine—a comparison with amitriptyline and placebo in healthy men

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1 The cardiovascular and anticholinergic effects of femoxetine and amitriptyline were compared with those of placebo in a double-blind cross-over trial in 12 healthy men. The daily doses administered were therapeutic: 600 mg femoxetine and 150 mg amitriptyline. Duration of treatment with each drug was 13 days.
2 The statistically significant effects on systolic time intervals and ECG comprised a larger decrease of QS_2 index during femoxetine than during amitriptyline, and an increase of PEP/LVET ratio and QRS duration by amitriptyline. These results suggest that femoxetine and, to a lesser extent, amitriptyline increase contractility compared with placebo, and amitriptyline, but not femoxetine, causes delay in intracardiac conduction.
3 The effects of amitriptyline on the systolic time intervals are difficult to interpret because of the changes in heart rate and intracardiac electrical conduction caused by the drug. These problems of interpretation are discussed.
4 No significant changes in blood pressure were observed. The heart rate during both femoxetine and amitriptyline periods was significantly faster than during the placebo period, amitriptyline causing a significantly greater increase.
5 Salivary secretion was decreased more by amitriptyline (26%) than by femoxetine (8%), the latter being not significantly different from placebo. Femoxetine tended to increase pupil diameter and amitriptyline to increase accommodation near point, but no visual disturbances were reported on any treatment. Symptoms such as dry mouth, constipation and sedation were significantly less frequently reported during femoxetine than during amitriptyline treatment.

Keywords 5-HT-uptake inhibition femoxetine systolic time intervals anticholinergic effect volunteers

Introduction

Treatment of depressive illness with tricyclic antidepressants may cause unwanted cardiovascular effects such as hypotension and tachycardia (Glassman & Bigger, 1981; Vohra *et al.*, 1975a,b), prolongation of intracardiac conduction (Burrows *et al.*, 1977) and possibly impairment of left ventricular function (Cokkinos *et al.*, 1976; Burgess *et al.*, 1979). In addition, many of the antidepressants currently available have marked anticholinergic activity which can cause dry mouth, visual disturbance, constipation, difficulty in micturition, and alteration in heart rate (Kolk *et al.*, 1978).

Femoxetine, a phenylpiperidine derivative, is a selective inhibitor of neuronal reuptake of 5-hydroxytryptamine. In contrast to the tricyclic

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antidepressants, femoxetine has only a weak inhibitory effect on noradrenaline uptake into peripheral organs, and has little or no central and peripheral anticholinergic action (Buus Lassen *et al.*, 1975). The clinical efficacy of femoxetine is comparable with that of amitriptyline and desipramine (Dahl *et al.*, 1982; Tamminen *et al.*, 1982; Ahlberg *et al.*, 1982) and it is believed to have little effect on the cardiovascular system (Nielsen, 1982).

The study reported here was a double-blind cross-over comparison of the cardiovascular and anticholinergic effects of multiple doses of femoxetine with doses of amitriptyline and placebo in healthy men.

Methods

Twelve healthy male volunteers gave written consent to participation in the study, which was approved by an independent ethics committee. The subjects were aged 20 to 30 years, weight 55 to 78 kg, and height 170 to 191 cm. All were normal on clinical history, physical examination, electrocardiogram, haematological and biochemical screening, urine analysis and Australia antigen.

The study was of double-blind, randomised, cross-over design in which the treatments were given for 13-day periods with one drug-free day between treatments. All three treatments were identical in appearance, and a complex escalating dose regime was used during the first 4 days of each treatment period. The final doses of each treatment were:

A.	Femoxetine 100 mg enteric coated tablets	200 mg 400 mg	morning evening
B.	Amitriptyline 25 mg tablets	150 mg	evening
C.	Placebo tablets	2 6	morning evening

During treatments A and B, additional placebo tablets were given as necessary to maintain double masking.

Tablets were dispensed in Dosett containers (Cow and Gate Ltd) containing 1 week's supply. The volunteers were asked to take the morning dose between 08.00–10.00 h and the evening dose between 20.00–22.00 h, with meals. However, the morning dose of day 12 was not taken until the first meal following the pharmacodynamic and kinetic assessments.

Pharmacodynamic assessments

All assessments were performed between 09.00–11.00 h after an overnight total fast. Studies were done on day 12 and day 14 of the three treatment periods; the day 12 assessment was done before the morning dose of tablets and on day 14 no treatments were given.

Cardiovascular

Subjects rested supine for at least 10 min before any cardiovascular measurements were made. Heart rate was measured by palpation at the wrist and blood pressure by mercury-in-glass sphygmomanometer taking Phase V of the Korotkov sounds as the diastolic pressure. Systolic time intervals (STI) and ECG lead II at 100 mm s^{-1} and 20 mm mV^{-1} were obtained as described previously (Burgess *et al.*, 1979).

The recordings from each subject were shuffled and analysed 'blind' by a single observer. Ten cardiac cycles were measured and averaged for each determination of the STI, and five cycles were measured for each ECG. The STI measured were QS_2 interval and left ventricular ejection time (LVET); pre-ejection period (PEP) is QS_2 minus LVET. On the ECG, measurements were made of PR interval, QRS duration, QT interval and T wave amplitude; the height of the T wave was measured with respect to the point marked by the observer as the end of the QT interval for each cardiac cycle. The QS_2 interval, LVET, and QT interval on the ECG were corrected for heart rate using regression equations derived previously (Burgess *et al.*, 1978, 1979a; Bryson *et al.*, 1978):

$$QS_2 \text{ Index} = QS_2 + (1.2 \times \text{heart rate})$$
$$\text{LVET Index} = \text{LVET} + (1.1 \times \text{heart rate})$$
$$\text{QT Index} = \text{QT} + (1.7 \times \text{heart rate})$$

Autonomic activity

Salivary secretion was estimated by weighing in a collection pot the total amount produced by the subject during a 3 min period of sucking on an acid-flavoured sweet (Kingsley & Turner, 1974).

Pupil diameter was measured using a simple twin hole pupil gauge (Smith and Nephew Pharmaceuticals) with the subject looking through the gauge at a standard light source to which he had been exposed for at least 5 min.

Accommodation near point was determined using the UK Royal Air Force rule.

5-hydroxytryptamine concentrations

Before the start of treatment, and on day 14 of each treatment period, 5 ml venous blood was taken into EDTA tubes and stored at −20° C.

Whole blood concentration of 5-hydroxytryptamine (5-HT) was determined as previously described (Lund *et al.*, 1979).

Adverse effects

On day 14 of each treatment the volunteers were asked if they had had any symptoms during the previous 2 weeks.

Pharmacokinetic assessments

Assay of drug concentrations Before treatment and on days 7, 12 and 14 of each treatment period, 10 ml blood was taken before the morning dose of tablets. Samples were placed in heparinised glass tubes with caps lined with aluminium foil. The plasma was separated and stored at −20° C until analysis. Plasma concentrations of femoxetine and norfemoxetine were determined as previously described (Bechgaard & Lund, 1977; Bechgaard *et al.*, 1978) with detection limits of < 5 ng ml^{-1} for femoxetine and < 3 ng ml^{-1} for norfemoxetine. Concentrations of amitriptyline and nortriptyline were measured by gas liquid chromatography with nitrogen detection.

Statistical analysis

Each variable was tested for normality of distribution using the Chi squared principle. Analysis of variance was then performed for each variable. Non-parametric analysis of variance (Friedman) was used if one or more of the measurements was not normally distributed. If analysis of variance yielded a significant result, paired *t*-tests were carried out if the distribution was normal in both treatment groups, and the paired Wilcoxon test was used if one or both were not normally distributed. In addition, delta-values (active treatment minus placebo) were tested for femoxetine against amitriptyline for day 12 and day 14 separately.

Table 1 Effects on pulse rate, blood pressure, ECG and systolic time intervals in healthy men of femoxetine and amitriptyline compared with placebo (* = $P < 0.05$ when compared with placebo, QTI = QT + 1.7 HR, $QS_2I = QS_2 + 1.2$ HR, LVETI = LVET + 1.1 HR, HR = heart rate)

	Analysis of variance P *value*	*Femoxetine (drug-placebo) mean (s.d.)*		*Amitriptyline (drug-placebo) mean (s.d.)*		*Placebo mean (s.d.)*		*Significance of change (P) (femoxetine compared with amitriptyline* P *value*	
		Day 12	*Day 14*	*Day 12*	*Day 14*	*Day 12*	*Day 14*	*Day 12*	*Day 14*
Blood pressure									
systolic	—	+3	−2	+11	+4	120	124	—	—
diastolic	—	−5	−1	+9	+5	70	71	—	—
Heart rate (beats min^{-1})	< 0.001	+8.5* (6.4)	+9.1* (7.5)	+24.5* (14.7)	+20.1* (12.0)	63.8 (7.4)	65.6 (8.9)	< 0.01	< 0.05
Effect upon the ECG									
PR interval (ms)	—	−2	−2	+7	+4	138 (17)	140 (21)	—	—
QRS (ms)	< 0.001	+0.3 (3.4)	+0.4 (5.0)	+4.6* (4.6)	+6.0* (4.8)	85 (10)	85 (8)	< 0.05	< 0.01
QTI (ms)	—	+7	0	0	−5	500 (12)	501 (16)	—	—
T-wave height (mm)	< 0.001	−1.5 (2.4)	−2.3* (2.4)	−1.5* (2.4)	−3.4* (2.0)	7.7 (1.9)	8.6 (2.4)	—	—
Effect upon the STI									
QS_2I (ms)	< 0.01	−8.8 (18)	−12.1* (11)	−4.4 (14)	−6.5* (9)	479 (24)	480 (16)	—	—
LVETI (ms)	< 0.05	−6.16 (11)	−8.33 (13)	−5.18 (15)	−9.58 (12)	361 (17)	364 (15)	—	—
PEP (ms)	—	−4	−4	−2	+1	112 (14)	110 (11)	—	—
PEP/LVET × 10^3	< 0.05	+7.83 (43)	+5.58 (44)	+31.2 (53)	+39.2* (64)	383 (52)	376 (58)	—	< 0.05

The null hypothesis was rejected when $P < 0.05$, but only tentative conclusions were drawn if this level of probability was not reached on both day 12 and day 14.

Results

One subject dropped out because of adverse effects of amitriptyline, and was replaced.

Cardiovascular effects (Table 1)

The statistically significant effects were:
a. Amitriptyline and femoxetine increased heart rate by a mean of 22 and 9 beats min^{-1} respectively, compared with placebo.
b. Amitriptyline increased QRS duration by a mean of 5 ms compared with placebo and femoxetine.
c. Amitriptyline decreased (2.5 mm average), and femoxetine tended to decrease (1.9 mm average) T-wave height compared with placebo.
d. Amitriptyline increased PEP/LVET ratio compared with both femoxetine and placebo.

Autonomic effects (Table 2)

The statistically significant effects were a decrease in salivary secretion of 26% by amitriptyline and a decrease of 8% by femoxetine compared with placebo; an increase in pupil diameter by femoxetine; and a trend towards increase in accommodation near point by amitriptyline.

Concentrations of drugs and 5-HT (Table 3)

Steady state plasma concentrations of femoxetine and its metabolite ranged from below detection limit to 99 ng ml^{-1} femoxetine and to 24 ng ml^{-1} norfemoxetine, the medians being 11 and 5 ng ml^{-1} for femoxetine and norfemoxetine respectively. Amitriptyline plasma concentration ranged from 21–135 ng ml^{-1} (median = 61) and the corresponding range for nortriptyline was 28–110 ng ml^{-1} (median = 50). The largest decrease of 5-HT in whole blood was observed during femoxetine treatment: the median concentrations during each treatment period of femoxetine, amitriptyline and placebo were 0.02, 0.05 and 0.09 μg ml^{-1} respectively.

For one subject who had femoxetine and norfemoxetine plasma concentrations below detection limit on both days 12 and 14, the 5-HT concentrations in whole blood were 0.03, 0.05 and 0.10 μg ml^{-1} after femoxetine, amitriptyline and placebo periods respectively. The 5-HT concentration in three other subjects was also decreased to 0.01, 0.02 and 0.05 μg ml^{-1} during the femoxetine period, even though the drug and metabolite concentrations were below the limit of detection on one of the assessment days.

Adverse effects (Table 4)

Amitriptyline caused the expected anticholinergic effects and sedation. Femoxetine caused more side effects than placebo, notably dry mouth in three subjects and nausea in two, but was better tolerated than amitriptyline.

Table 2 Effect on autonomic activity in healthy men of femoxetine and amitriptyline compared with placebo (* = $P < 0.05$ when compared with placebo)

	Femoxetine (drug-placebo) mean (s.d.)		*Amitriptyline (drug-placebo) mean (s.d.)*		*Placebo mean (s.d.)*		*Significance of change (P) (femoxetine compared with amitriptyline)*	
	Day 12	*Day 14*	*Day 12*	*Day 14*	*Day 12*	*Day 14*	*Day 12*	*Day 14*
Salivary secretion (g) (stimulated)	−1.47* (1.8)	−1.41 (3.1)	−4.52* (3.5)	−4.34* (2.8)	15.0 (6.8)	17.7 (4.1)	< 0.01	< 0.01
% of placebo value	91%*	92%*	73%*	74%*	—	—		
Pupil diameter (mm)	+0.46 (0.8)	+0.38* (0.5)	−0.08 (1.0)	0.00 (0.6)	5.4 (0.9)	5.1 (0.9)	< 0.01	< 0.05
Accommodation near point (cm) Left	+0.3 (2.5)	+1.0 (4.0)	+2.6* (1.3)	+1.0 (2.6)	11.6 (2.7)	11.8 (3.4)	< 0.01	—
Right	+0.4 (2.8)	+1.5 (3.9)	+1.2 (3.6)	+0.8 (2.9)	11.4 (2.0)	11.8 (3.8)	—	—

Table 3 Plasma concentration of active drug and metabolite together with whole blood concentration of 5-HT (* day 0 = first day of study period; BD = below detection; fem = femoxetine; norf = norfemoxetine; ami = amitriptyline; nort = nortriptyline; pla = placebo)

Subject	*Femoxetine (ng ml^{-1})*				*Amitriptyline (ng ml^{-1})*				*5-HT (μg ml^{-1})*					
	Day 12		*Day 14*		*Day 12*		*Day 14*		*Fem*		*Ami*		*Pla*	
	Fem	*Norf*	*Fem*	*Norf*	*Ami*	*Nort*	*Ami*	*Nort*	*Day 0*	*Day 14*	*Day 0*	*Day 14*	*Day 0*	*Day 14*
1	13	10	18	7	110	92	93	90	—	0.02	0.06*	0.06	—	0.12
2	BD	BD	BD	BD	25	29	21	29	—	0.03	0.10*	0.05	—	0.10
3	15	11	BD	BD	52	53	55	58	—	0.03	—	0.04	0.11*	0.08
4	65	23	99	24	120	74	135	76	—	0.01	—	0.01	0.08*	0.06
5	9	4	10	BD	88	47	72	44	0.15*	0.03	—	0.05	—	0.12
6	14	5	8	BD	37	28	40	30	0.08*	0.01	—	0.03	—	0.08
7	BD	BD	6	BD	53	36	55	36	—	0.02	0.06*	0.05	—	0.07
8	11	6	8	BD	115	110	100	105	—	0.05	0.16*	0.05	—	0.09
9	BD	BD	19	13	26	36	36	39	—	0.01	—	0.03	0.10*	0.09
10	29	21	14	BD	72	58	66	54	—	0.01	—	0.03	0.07*	0.07
11	BD	BD	24	9	45	34	41	39	0.05*	0.05	—	0.05	—	0.08
12	29	16	29	20	74	88	75	91	0.07*	0.01	—	—	—	0.09
Median (drug/ metabolite)	11/5				61/50				—	0.02	—	0.05	—	0.09
Range (drug/ metabolite)	BD–99/BD–24				21–135/28–110									

Table 4 Adverse effects reported after each of the three treatment periods in response to non-directed question (* in one of the cases, relation to treatment was doubtful as judged by the investigator before the identity of the treatment was known)

Adverse event	Number of volunteers reporting AMI	FEM	PLA
Dry mouth	12	3	–
Drowsiness	4	2	2
Tiredness/falling asleep	3	2*	–
Constipation	3	–	–
Urination difficulties	1	–	–
Nausea	–	2	–
Sedation	5	–	–
Dizziness/headache	2*	2*	2
Tremor	1	1	–
Vivid dreams	–	1	–
Other effects	10	–	–

Discussion

Heart rate and blood pressure

Heart rate was increased by amitriptyline compared with placebo; this effect is consistent with previous studies (Burgess *et al.*, 1979a; Peet *et al.*, 1977; Ziegler *et al.*, 1977). It has generally been assumed that the increase in heart rate seen during treatment with amitriptyline is caused by its anticholinergic action, but other possibilities include a peripheral effect of the drug on adrenergic function, a central action on vasomotor regulation, and a reflex response to reduced peripheral resistance caused by alpha-adrenoceptor antagonism (U'Prichard *et al.*, 1978). Femoxetine increased heart rate compared with placebo, but significantly less so than that during amitriptyline. The mechanism of femoxetine's effect on heart rate might include the central effects of 5-HT and NA uptake inhibition and a peripheral effect on serotonergic function.

Blood pressure was not affected by either of the active treatments in this study, though it should be noted that all measurements were made with the subjects supine. This is consistent with previous studies of amitriptyline (Burgess *et al.*, 1979a).

Systolic time intervals (STI)

Femoxetine, and to a lesser extent amitriptyline, shortened QS_2 index in comparison with placebo. This shortening of QS_2 index occurred in spite of prolongation of QRS in the case of amitriptyline, and implies that both drugs increased myocardial contractility (Lewis *et al.*, 1977). Tricyclic antidepressants are widely believed to have depressant rather than stimulant effects on contractility, but there is little evidence that this is so when the drugs are used in therapeutic doses (Glassman & Bigger, 1981) and our results for amitriptyline and QS_2 index are concordant with those of Burgess and co-workers (1979a). Most reports on studies with antidepressant drugs on STI have emphasised the effect of the drugs on PEP and PEP/LVET ratio (Burgess *et al.*, 1978, 1979a; Burckhardt *et al.*, 1978; Taylor & Braithwaite, 1978) and some authors have entirely omitted the results of QS_2 measurements (Thayssen *et al.*, 1981).

LVET index was not significantly altered by amitriptyline or femoxetine. Our results for amitryptyline are in agreement with those of Burgess and co-workers (1979a).

Pre-ejection period was not altered by either active treatment, which at first sight appears discordant with previous reports that amitriptyline increases pre-ejection period (Burgess *et al.*, 1978, 1979a). In these previous studies, however, STI were corrected for heart rate using the original regression equations of Weissler (Weissler *et al.*, 1968) who derived their regression slope values from single measurements made in each of a large number of resting subjects. These regression slopes are very similar to those obtained by Johnson and co-workers (1981) during infusion of isoprenaline, suggesting that the marked variability in resting heart rate in the study of Weissler *et al.* (1968) was associated with wide inter-individual variation in cardiac sympathetic drive. In studies of the haemodynamic action of drugs the aim is generally to identify changes in contractility independent of changes in heart rate, and the equations of Weissler *et al.* are unsuitable for this purpose because they consistently overcorrect for heart rate increases (Johnson *et al.*, 1981). It is now clear that pre-ejection period need not be corrected for change in heart rate (Johnson *et al.*, 1981; Spodick, 1977). If the regression equation of Weissler *et al.* (PEP index = PEP + (0.4 × heart rate)) were applied to our data, the rate corrected value of PEP would increase by 2.4 ms for femoxetine and 6.4 ms for amitriptyline compared with placebo, since the heart rates (measured from the STI traces) on the active drugs were 6 and 16 beats min^{-1} respectively greater than placebo. We suggest that previous reports that tricyclic antidepressants prolong the pre-ejection period are based partly on the use of an inappropriate method of correction for

increase in heart rate and partly on failure to take account of the possible effects of prolongation of intracardiac conduction on PEP.

Similar considerations must apply to the interpretation of our results for PEP/LVET ratio, which showed a tendency to increase during amitriptyline treatment: if pre-ejection period is unaffected by increase in heart rate, but LVET is shortened (Burgess *et al.*, 1979a; Johnson *et al.*, 1981), then the ratio PEP/LVET must inevitably increase as heart rate rises, independently of any drug effects on contractility. Cokkinos and coworkers (1976) showed that PEP/LVET was indeed increased when heart rate rose following atropine administration.

In this study, we corrected the STI for heart rate using the same regression equations for all subjects. Kelman and colleagues (1981) have advocated the use of regression equations derived separately for each subject; it is likely, but unproven, that this would reduce the variability in STI attributable to differences in heart rate alone, and this would increase the power of any study to detect drug-induced changes in the STI. Our use of single regression equations for all subjects may therefore have led to some false negative results, but is unlikely to have caused false positive ones.

The results for STI in this study suggest that neither amitriptyline nor femoxetine has major haemodynamic effects in the doses used, but the reduction in QS_2 index by both drugs is consistent with a minor increase in contractility. It is not possible to say whether this is a direct effect of the drugs or whether it is mediated through increased sympathetic drive. The intriguing possibility arises that amitriptyline might have caused greater shortening of QS_2 index and perhaps also of pre-ejection period had it not also caused prolongation of QRS duration; increased QRS duration is caused by slowing of intraventricular conduction, which will prolong all the STI.

ECG

Neither drug had any significant effect on PR interval. QRS duration was consistently increased by amitriptyline compared with both femoxetine and placebo; femoxetine had no significant effect on this variable. These results are broadly in agreement with previous studies on tricyclic antidepressants (Burrows *et al.*, 1977).

Rate-corrected QT interval (QT index) was not affected by either active treatment compared with placebo. A transient decrease in QT interval after a single dose of amitriptyline 50 mg has been observed in normal volunteers (Burgess *et al.*, 1978). Thayssen *et al.* (1981) found no effect of either imipramine or nortriptyline on QT_C (QT_C = observed $QT/\sqrt{RR}$ interval) in elderly depressed patients. In contrast, other workers have demonstrated persistent prolongation of QT_C during treatment with imipramine (Kantor *et al.*, 1978; Giardina *et al.*, 1979) and desipramine (Veith *et al.*, 1980), which may reflect the quinidine-like activity of imipramine and its metabolite (Glassman & Bigger, 1981). In our volunteers, plasma concentrations of amitriptyline and nortriptyline were well below 200 ng ml^{-1}, which is the level above which Vohra *et al.* (1975) consistently observed prolongation of H-V conduction.

As with the systolic time intervals, there is a major methodological problem in correcting observed QT interval for change in heart rate. Bazett's formula, which is the correction device used in all the studies referred to above, substantially overcorrects for change in heart rate (Staniforth, 1983) and in this study we have used a simple linear regression equation (Bryson *et al.*, 1978). It is quite possible that some of the reports of prolongation of QT_C during treatment with tricyclic antidepressants were based on an inappropriate method of correcting for change in heart rate.

T-wave amplitude was significantly reduced by amitriptyline compared with placebo, and by femoxetine on day 14 only. It is possible that these effects on T-wave amplitude resulted simply from an increase in heart rate, but a change in the T-wave irrespective of heart rate would be expected in the case of amitriptyline, which significantly prolonged QRS duration; altered depolarisation must lead to some alteration in repolarisation.

Autonomic activity

Both drugs caused a decrease in salivation, amitryptyline being more powerful (26% reduction) than femoxetine (8% reduction). Although the greater effect of amitriptyline than femoxetine in reducing salivation is consistent with the greater anticholinergic potency of amitryptyline, it may also reflect the greater potency of amitriptyline in blocking α-adrenoceptors (Buus Lassen *et al.*, 1975; U'Prichard *et al.*, 1978). The results of the salivation test are in agreement with those obtained previously in volunteers (Clemmensen *et al.*, 1984) and patients (Ghose *et al.*, 1977).

Pupil diameter tended to be increased by femoxetine but not by amitriptyline treatment. Since femoxetine had little anticholinergic effect in the saliva flow test, its mydriatic action prob-

ably reflects an increase in adrenergic tone in the iris. In the case of amitriptyline, anticholinergic and adrenergic effects may have balanced each other, leading to no change in pupil diameter.

The tendency for amitriptyline to impair accommodation is a further reflection of its anticholinergic action. The observation that femoxetine caused little change in accommodation near point is consistent with previous findings in volunteers and patients (Jeppesen & Fledelius, 1985).

Spontaneously reported adverse effects due to anticholinergic activity (dry mouth, constipation, difficulty in micturition) were reported 3 and 16 times during femoxetine and amitriptyline periods respectively, reflecting the lower anticholinergic potency of femoxetine. The results are consistent with side effects observed in therapeutic studies (Dahl *et al.*, 1982; Tamminen *et al.*, 1982; Ahlberg *et al.*, 1982).

Plasma concentrations of drugs and 5-HT

Plasma concentrations of amitriptyline and nortriptyline were mostly within the therapeutic range and were consistent within subjects, suggesting that compliance was good. Plasma concentrations of femoxetine and norfemoxetine, in contrast, showed marked intersubject variability: they were consistently below the limit of detection in one subject and were close to it in three subjects. Similar variability has been observed previously (Dahl *et al.*, 1982) and measurement of plasma femoxetine concentrations is evidently not a satisfactory indication of compliance. Measurement of whole blood concentrations of 5-HT indicates at least fair compliance with femoxetine treatment: 5-HT concentrations fell in all 12 subjects compared with values obtained during placebo treatment. Amitriptyline also reduced 5-HT concentrations, but to a lesser extent than did femoxetine.

Conclusions

In this study neither amitriptyline nor femoxetine had any major haemodynamic effects, but their effects on the STI suggest enhancement rather than depression of contractility. Amitriptyline increased heart rate substantially and femoxetine increased it slightly. Amitriptyline prolonged QRS duration, which is compatible with its Class 1 antidysrhythmic effect. Femoxetine was better tolerated than amitriptyline, particularly with respect to autonomic effects.

These results encourage the hope that femoxetine will prove to be free from major cardiovascular effects in clinical use. However, this remains to be tested when the drug is used widely in the treatment of depressed patients.

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