

PRELIMINARY ASSESSMENT OF FLUTIOREX, A NEW ANORECTIC DRUG, IN MAN

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1 The effects of \pm -flutiorex, a new anorectic agent, on food intake, the sympathetic nervous system and the central nervous system were compared to those of fenfluramine and a placebo in a double-blind trial involving six healthy volunteers.

2 Flutiorex exerts a significant anorectic effect and was shown to be approximately twice as potent as fenfluramine in this regard.

3 Flutiorex induces a definite α -adrenergic sympathomimetic stimulation as was shown by a rise in systolic blood pressure and the development of marked mydriasis.

4 Flutiorex is a central nervous system stimulant producing an increase in critical flicker frequency. It does not, however, influence psychomotor coordination as reflected in the pursuit rotor test.

5 Serial determinations of blood and urine levels of flutiorex and its deethylated metabolite, norflutiorex, showed that flutiorex is rapidly absorbed and deethylated, accumulates in large quantities in the tissues and, like its metabolite, is excreted in the urine in very small quantities. Blood levels of norflutiorex appear to remain elevated longer than those of flutiorex.

Introduction

Flutiorex, or \pm -1-(3'-trifluoromethylthio-phenyl)-2-ethylamino-propane (Figure 1, 1a) is a new anorectic drug, the chemical structure of which closely resembles that of fenfluramine (Figure 1, 2a). After experimental pharmacological studies showed that flutiorex significantly reduced food intake in rats, its anorectic properties being twice as potent as those of fenfluramine (Giudicelli, Lefèvre, Jalfre, Branceni & Najer, 1975), preliminary human studies on volunteers were undertaken which confirmed the anorectic properties of flutiorex in man.

These studies also showed that certain similarities exist between the metabolism of flutiorex and that of fenfluramine since the former is to a large extent deethylated into norflutiorex (Figure 1, 1b) while the latter forms norfenfluramine via the same reaction (Figure 1, 2b) (Beckett & Brookes, 1967).

We now present the results obtained in a double-blind study of the effects of flutiorex (20 mg), fenfluramine (40 mg) and a placebo on food intake, sympathetic nervous function and the central nervous system in six healthy volunteers.

Methods

Six healthy volunteers, five male and one female, aged 20-45 years and all weighing from 55-73 kg, except for one male subject who weighed 112 kg, were given oral doses of flutiorex (20 mg), fenfluramine (40 mg) and a placebo in random order at weekly intervals. Randomization was based on a latin square design under double-blind conditions. None of the subjects was receiving any other medication at the time of the trial.

Parameters investigated

The following parameters were investigated: pulse rate (PR), systolic (SBP) and diastolic (DBP) blood pressure (measured by means of a pneumatic cuff), pupillary diameter (always measured in the same light intensity), critical flicker frequency (CFF) using the technique described by Turner (1971) and Houghton, Latham & Richens (1973), psychomotor performance (PRP) (measured by the 'pursuit rotor' MK 3/T, Forth Instruments Ltd) and food intake. In addition, blood levels (both plasma and red blood cells) and urinary

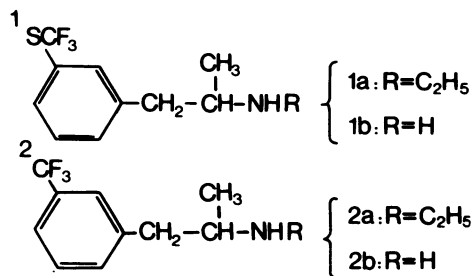


Figure 1 The structural formulae of flutiorex (1a), fenfluramine (2a), norflutiorex (1b) and norfenfluramine (2b).

excretion of flutiorex and norflutiorex were determined.

Experimental procedure

The experimental protocol was as follows: after a very light breakfast consisting of one slice of bread and a glass of water at 07 h 30 min, the volunteer arrived at the laboratory at 08.00 h, rested for 0.5 h, underwent all the control tests between 08 h 30 min and 09.00 h, had a blood sample taken, emptied his bladder and was immediately given the drug (09.00 h). Blood samples were again taken 0.5, 1, 3 and 6 h later and urine was collected 0.5, 1, 2, 4, 6, 9, 12, 24 and 48 h after drug intake. The volume and pH (the latter being voluntarily uninfluenced) of each urine sample were measured.

The anorectic effect of the drugs was assessed by the weight of food (standardized ham and cheese sandwiches) ingested 4.5 h after administration.

PR, SBP and DBP, PD, CFF and PRP were measured immediately prior to, and 1, 2, 3, 4, 6 and 9 h after drug intake. The volunteers were also asked to fill out a questionnaire as to their general tolerance to the drugs during the trial (incidence of side-effects, e.g. chilliness, dizziness, dryness of the mouth, nausea, diarrhoea, headache, etc. . .), their appetite on the evening following drug intake and how they slept that same night.

No tea, coffee, alcoholic beverages or smoking were allowed throughout the entire trial period.

Assay of flutiorex and norflutiorex by gas chromatography in plasma, red blood cells and urine

Gas chromatography: a Becker Gas Packard chromatograph with a flame ionization detector was used. The column (2 m long \times 3 mm i.d.) was of glass (Carbowax 20M 10% on 80-100 mesh

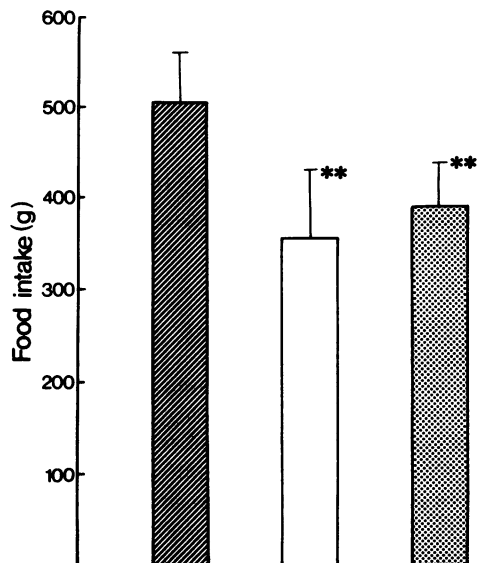


Figure 2 Comparative effects (mean \pm s.e. mean) of placebo (▨), flutiorex (20 mg, □) and fenfluramine (40 mg, ▩) on food intake in man, ** significantly different from placebo ($P < 0.01$).

Chromosorb coated with 3% potassium hydroxide) and conditioned at 140°C in a stream of nitrogen for 24 h before use. The instrument settings were as follows: temperature, injection port 200°C and detector port 200°C; gas flow rates, hydrogen 30 ml/min, nitrogen 30 ml/min and air 40 ml/min; temperature programming: initial 135°C, final 165°C, increase rate: 2°C/min after an initial isotherm period of 1 minute.

Plasma: plasma (10 ml) was made alkaline by adding 2N sodium hydroxide (1 ml) and extracted by shaking with diethyl ether (10 ml) and 100 μ l of internal standard solution (dexamphetamine hydrochloride in diethyl ether, 10 μ g/ml) in a mechanical shaker for 10 minutes. After centrifugation at 3000 rev/min, the ether phase was removed and carefully concentrated to approximately 50 μ l with a slow stream of nitrogen. 2 μ l were injected in the chromatograph for analysis.

Red cells: the red blood cells (5 ml) were haemolyzed by placing them in a freezer with distilled water (10 ml) for 10 minutes. The haemolysate (10 ml) was then taken and treated in the same manner as the plasma.

Urine: urine (5 ml) was made alkaline by adding 2N sodium hydroxide (2 ml) and extracted by

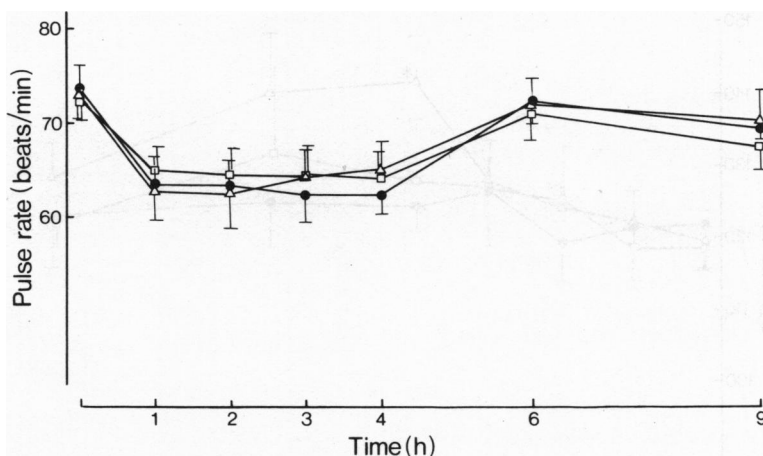


Figure 3 Comparative effects (mean \pm s.e. mean) of flutiorex (20 mg, Δ), fenfluramine (40 mg, \square) and a placebo (\bullet) on pulse rate over the 9 h period following drug administration.

shaking in a mechanical shaker for 10 min with diethyl ether (20 ml) and 100 μ l of the same internal standard solution used for the plasma. After centrifugation at 3000 rev/min, the organic layer was transferred to a centrifuge tube containing 0.5N hydrochloric acid (5 ml) and the mixture was shaken for 5 min with the mechanical shaker. After a second centrifugation (3000 rev/min), the organic layer was discarded. The residual aqueous phase was made alkaline by adding 2N sodium hydroxide (2 ml) and extracted with diethyl ether (10 ml) by shaking with the mechanical shaker for 10 minutes. After a third centrifugation (3000 rev/min), the ether layer was removed and carefully concentrated to approximately 50 μ l with a slow stream of nitrogen. For analysis, 2 μ l were injected into the chromatograph.

The threshold of detection of flutiorex and norflutiorex in plasma, red blood cells and urine was 2 ng/ml.

Drugs used

The drugs used were flutiorex hydrochloride and fenfluramine hydrochloride (20 mg and 40 mg respectively). Doses are expressed in terms of the salts.

Statistical analysis

Statistical analysis of the data was performed by means of the Student's *t*-test (paired comparisons with pre-drug values).

Results

Anorectic effect

Both flutiorex (20 mg) and fenfluramine (40 mg) significantly decreased food intake (Figure 2) but there was no significant difference between the two drugs in this respect.

Anorexia was still obvious in three of the six subjects at dinner time with both drugs.

Pulse rate

Neither flutiorex nor fenfluramine had any effect on pulse rate (Figure 3).

Blood pressure

Figure 4 shows that flutiorex raised SBP between 4 and 6 h following its administration, the rise being significant after 4 hours. DBP followed a similar course. Two of the six volunteers had a rise in SBP to 160 and 180 mmHg respectively, the latter being observed 6 h after drug intake in the subject whose weight was 112 kg. It is noteworthy that the SBP of this same subject rose to 190 mmHg with fenfluramine.

Pupillary diameter

Both fenfluramine and flutiorex significantly increased pupillary diameter as early as the second hour following drug administration and this effect lasted for at least 7 h (Figure 5). There was no

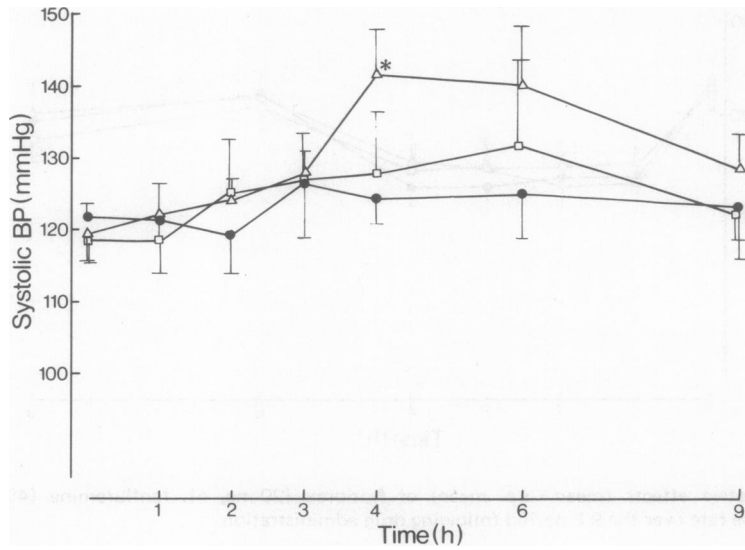


Figure 4 Comparative effects (mean \pm s.e. mean) of flutiorex (20 mg, Δ), fenfluramine (40 mg, \square) and a placebo (\bullet) on systolic blood pressure over the 9 h period following drug administration, * significantly different from pre-drug value ($P < 0.05$).

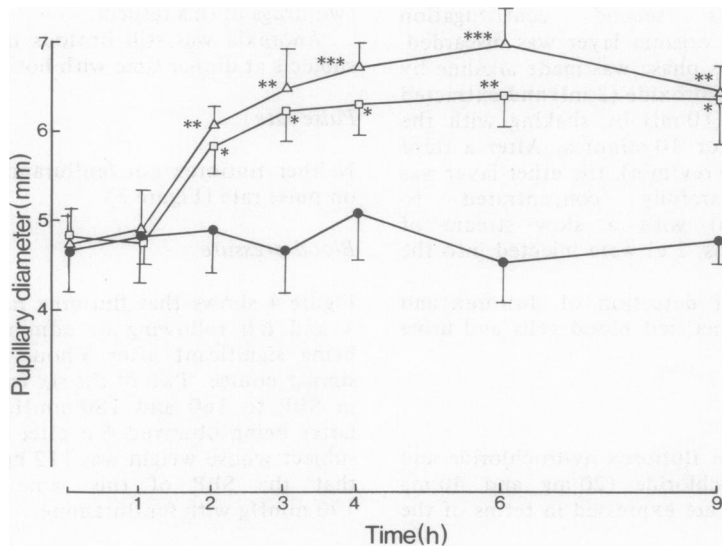


Figure 5 Comparative effects (mean \pm mean) of flutiorex (20 mg, Δ), fenfluramine (40 mg, \square) and a placebo (\bullet) on the pupillary diameter over the 9 h period following drug administration, * significantly different from pre-drug value ($P < 0.05$); ** significantly different from pre-drug ($P < 0.01$); *** significantly different from pre-drug value ($P < 0.001$).

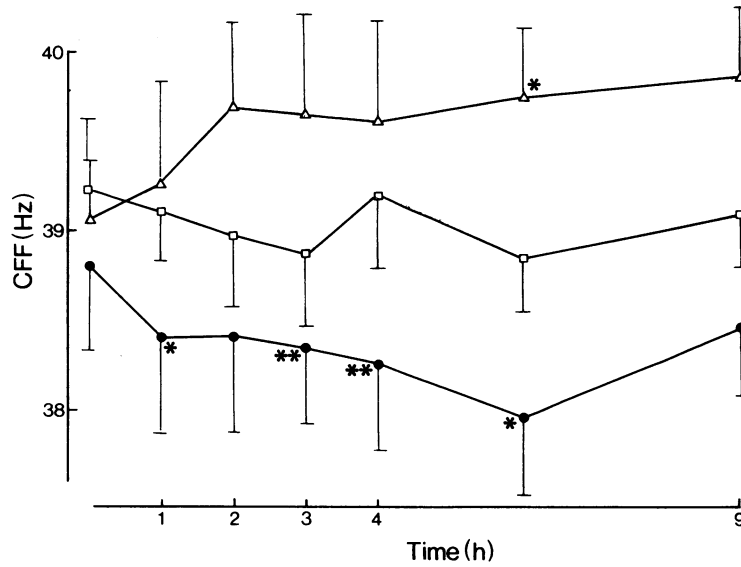


Figure 6 Comparative effects (mean \pm s.e. mean) of flutiorex (20 mg, Δ), fenfluramine (40 mg, \square) and a placebo (\bullet) on the critical flicker frequency (CFF) over the 9 h period following drug administration, * significantly different from pre-drug value ($P < 0.05$); ** significantly different from pre-drug value ($P < 0.01$).

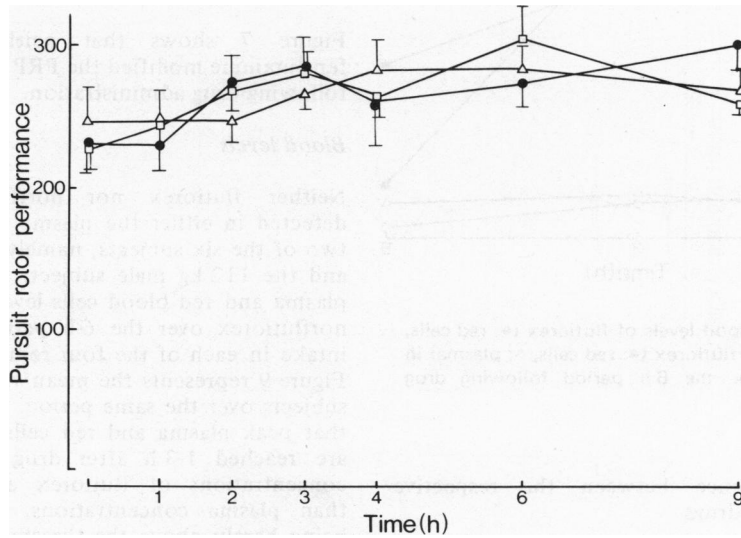


Figure 7 Comparative effects (mean \pm s.e. mean) of flutiorex (20 mg, Δ), fenfluramine (40 mg, \square) and a placebo (\bullet) on the 'pursuit rotor' performance (arbitrary units) over the 9 h period following drug administration.

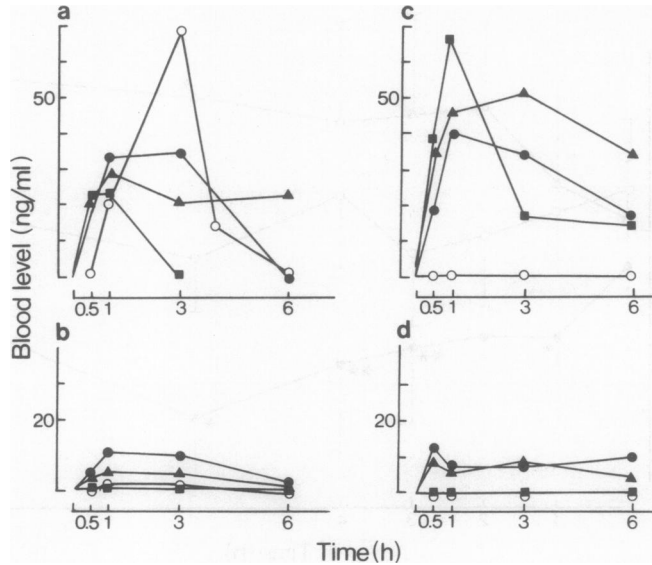


Figure 8 Blood levels of flutiorex (a: red cells, b: plasma) and norflutiorex (c: red cells, d: plasma) in four different subjects (●, ▲, ■, ○) over the 6 h period following drug administration.

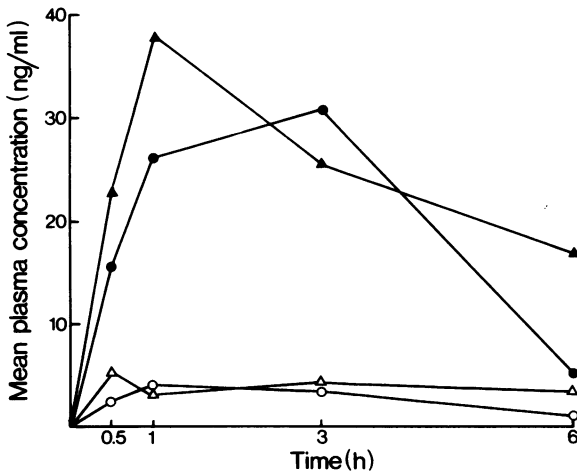


Figure 9 Mean blood levels of flutiorex (●: red cells, ○: plasma) and norflutiorex (▲: red cells, △: plasma) in four subjects over the 6 h period following drug administration.

significant difference between the respective effects of the two drugs.

Critical flicker frequency

With the placebo, the CFF decreased steadily throughout the whole duration of the trial while

with fenfluramine there was no change. With flutiorex however, the CFF increased perceptibly, this increase being significant 6 h after administration of the drug (Figure 6).

Pursuit rotor performance

Figure 7 shows that neither flutiorex nor fenfluramine modified the PRP over the 9 h period following drug administration.

Blood levels

Neither flutiorex nor norflutiorex could be detected in either the plasma or the red cells of two of the six subjects, namely the female subject and the 112 kg male subject. Figure 8 shows the plasma and red blood cells levels of flutiorex and norflutiorex over the 6-h period following drug intake in each of the four remaining subjects and Figure 9 represents the mean values for these four subjects over the same period. These figures show that peak plasma and red cells levels of flutiorex are reached 1-3 h after drug intake. Red cells concentrations of flutiorex are 4-8-fold higher than plasma concentrations, the latter usually being barely above the threshold of sensitivity of the method used. Peak plasma and red cells levels of norflutiorex are reached early (0.5-1 h after drug administration) and remain elevated longer than those of flutiorex. Red cells concentrations

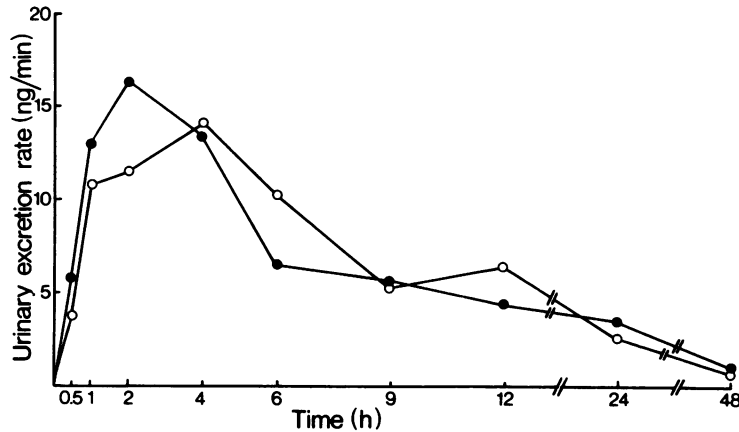


Figure 10 Mean urinary excretion rate of flutiorex (●) and norflutiorex (○) in six subjects over the 48 h period following drug administration.

of norflutiorex are 3-10-fold higher than plasma concentrations.

Urinary excretion

Figure 10 shows the mean excretion rate of flutiorex and its metabolite over a 48-h period in the six subjects. No attempt was made to control urinary pH. Excretion begins early for both substances but is quantitatively very low since it accounts for only 0.081% of the dose ingested in the first 24 h (Table 1) and for only 0.096% in the first 48 hours.

General tolerance

The most common side effects encountered with flutiorex, in the order of decreasing incidence, were chilliness (5/6), a feeling of ebriety (4/6), yawning (3/6), dizziness (2/6) and contraction of

the masseters (2/6). All these side-effects reached their maximum intensity 2-4 h after drug intake. Sleep during the night following the trial was normal in five subjects but one complained of insomnia and severe headache. The side-effects observed with fenfluramine were qualitatively identical, occurred with the same frequency but seemed to be slightly less pronounced.

Discussion

Determination of blood levels of flutiorex in the four subjects in whom the substance was detectable showed that firstly, it is very rapidly absorbed since peak levels were practically reached by the end of the first hour following administration, and secondly, that this peak level is maintained virtually unchanged until at least the third hour. Flutiorex thus appears to be absorbed

Table 1 Urinary excretion of flutiorex and norflutiorex over a 24 h period following flutiorex intake (20 mg)

Subject	Urinary excretion (µg/24 h) of			24 h excretion (% of the dose ingested)
	Flutiorex	Norflutiorex	Flutiorex + norflutiorex	
♂	6.27	8.84	15.11	0.075
♂	9.32	17.32	26.64	0.133
♂	8.72	9.62	18.34	0.092
♂	14.62	7.42	22.04	0.110
♂	3.32	3.66	6.98	0.035
♀	6.67	2.01	8.68	0.043
Mean	8.15	8.14	16.29	0.0815
s.e. mean	1.55	2.20	3.11	0.015

faster than fenfluramine since peak levels of the latter are reached only 2-3 h after administration. However, once reached, peak levels of fenfluramine remain unchanged until around the 8th hour (Campbell, 1970).

Similarly to fenfluramine, flutiorex is highly liposoluble and rapidly accumulates in the tissues. Plasma levels are thus low and proportionally even lower than those of fenfluramine since peak values observed were 5 ng/ml after a dose of flutiorex (20 mg) instead of 63 ng/ml after a dose of fenfluramine (60 mg) (Campbell, 1970). Lastly, as for fenfluramine (Campbell, 1970), red cells levels of flutiorex were found to be higher than plasma levels, the ratio being 4-8:1 for flutiorex but only around 1.5:1 for fenfluramine (Campbell, 1970).

Deethylation is, among others (Beckett, Coutts & Ogunbona, 1973), one of the metabolic pathways by which fenfluramine is broken down in man (Beckett & Brookes, 1967) and our results show that this is also the case for flutiorex. However, for the latter this transformation appears to take place very early since norflutiorex can be detected in the blood as little as 30 min after drug intake and peak plasma and red cells levels are reached by the end of the first hour while norfenfluramine can only be detected later and peak levels are reached after approximately 3 h (Campbell, 1970). This rapid metabolism raises the problem of knowing whether flutiorex is deethylated by intestinal bacteria even before the liver has a chance to intervene. However, as is often the case with highly liposoluble substances, there are marked individual variations in the rate of biotransformation; in one of the four subjects for example, norflutiorex was detected in neither the plasma nor the red cells and only determination of urinary levels was possible. From a quantitative standpoint, plasma and red cells levels of norflutiorex are virtually as high as those of flutiorex but they appear to remain elevated longer. The distribution volume of the drug for the four subjects, calculated when peak levels of both flutiorex and norflutiorex were reached, was from 220-300 litres, thus confirming a high degree of tissue fixation.

In two subjects, blood levels of flutiorex and norflutiorex were below the sensitivity threshold of the method used and could therefore not be determined. This can probably be related to poor absorption in the female volunteer, who incidentally had only very mild side-effects, and to marked dilution and/or a high degree of tissue accumulation in the 112 kg male subject.

Urinary excretions of flutiorex and norflutiorex were qualitatively and quantitatively identical. However, although the other urinary metabolites

of flutiorex have not been measured, it should be stressed that the absolute quantities of flutiorex and norflutiorex excreted in 24 h were very low (less than 0.1% of the dose administered), even lower than for fenfluramine (Beckett & Brookes, 1967).

Our results clearly demonstrate that flutiorex (20 mg) and fenfluramine (40 mg) can produce statistically significant anorexia in normal human subjects. They confirm the experimental data showing that flutiorex is twice as potent as fenfluramine in reducing food intake in rats. Furthermore, it is likely that the anorectic properties of flutiorex would have appeared even more marked had they been assessed earlier, when blood levels were at their peak.

Flutiorex also exerts a definite α -adrenergic sympathomimetic effect. Although heart rate does not vary, blood pressure rises significantly 4 h after drug administration. This phenomenon, which was particularly marked in two of the six volunteers, is probably related to peripheral vasoconstriction. The sympathomimetic effect of flutiorex was also reflected in marked, bilateral and symmetrical mydriasis. This phenomenon, which is also observed with fenfluramine (Kramer, Rubicek & Turner, 1973), begins to develop towards the second hour, is most marked around the sixth hour and persists until at least the ninth hour following drug intake. Since blood levels of flutiorex are already very low after six hours, it may well be that mydriasis is largely due to its deethylated metabolite, as is the case with fenfluramine (Turner, 1970; Kramer *et al.*, 1973). Experiments are in progress to test this hypothesis.

In any case, the sympathomimetic activity of flutiorex appears to be clearly more pronounced than that of fenfluramine. The same is true of its effects on the central nervous system. Although neither flutiorex nor fenfluramine modified psychomotor coordination, as reflected in the pursuit rotor performance, the former significantly increases CFF, indicating substantial CNS stimulation, while the latter has no effect on CFF (Hill & Turner, 1967; Turner, 1971). While clearly distinguishing flutiorex from fenfluramine, the latter exerting mainly a sedative effect in therapeutic doses, this property likens flutiorex to other stimulant anorectic agents such as phenmetrazine and diethylpropion (Smart, Sneddon & Turner, 1967).

In summary, despite its structural similarities with fenfluramine, flutiorex differs from the latter in that its anorectic effect is twice as potent, and its α -adrenergic sympathomimetic effects and stimulant effects on the central nervous system are more pronounced.

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