DISTRIBUTION AND ACTION OF FLUACIZINE DURING PROLONGED ADMINISTRATION

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UDC 615.214.32.033

Quantitative spectrophotometric determination of fluacizine (10-[β-diethylaminopropionyl]-2-trifluomethyl-phenothiazine hydrochloride) in the organs and plasma of rats showed that after daily administration of the compound for 15 days its content in the brain and plasma increased but in the liver it did not change significantly. The ability of the preparation to abolish catalepsy induced in rats by tetrabenzine was weakened at this stage. The differences in the fluacizine concentrations in the brain, plasma, and liver and in the manifestation of its action observed in these experiments can be explained by an increase in the bound form of the compound and its accelerated transformation in the liver.

The study of the distribution and action of the new Soviet antidepressant fluacizine (10-[β-diethylaminopropionyl]-2-trifluomethyl-phenothiazine hydrochloride) in rats following a single dose has revealed a connection between the concentration of the compound in the liver, brain, and plasma, and its ability to abolish catalepsy induced by tetrabenazine [2].

It was therefore decided to continue the study of the distribution of fluacizine in rats following repeated daily administration of the compound and to compare it with the manifestations of its action.

EXPERIMENTAL METHOD

Male rats weighing 180-220 g were used. A solution of fluacizine hydrochloride in distilled water was injected intraperitoneally into the rats in a dose of 20 mg/kg and in a volume of 0.4 ml/100 g body weight daily for 15 days. Control animals received distilled water in the same volumes. The concentrations of unchanged fluacizine in the liver, brain, and plasma of the animals were determined quantitatively by the spectrophotometric method described earlier [2]. The fluacizine concentration in the blood plasma, brain, and liver was determined 15 and 30 min and 1, 2, 4, 6, and 24 h after a single dose and after administration for 15 days.

The action of fluacizine during prolonged administration was studied and compared with the action of a single dose by assessing its ability to abolish catalepsy induced in rats by tetrabenazine. Tetrabenazine was injected intraperitoneally in a dose of 6 mg/kg. The severity of the catalepsy was determined on a point scale [16]. Fluacizine was injected intraperitoneally in the same dose as for the study of its distribution, 30 min after the tetrabenazine, during established catalepsy.

EXPERIMENTAL RESULTS AND DISCUSSION

After prolonged intraperitoneal injection of fluacizine, as after a single dose, its highest concentrations were recorded in the liver of the rats, its concentration in the brain was much lower, and in the plasma it was extremely low. The highest concentrations of unchanged fluacizine were found in the plasma and liver 30 min, and in the brain 1 h, after administration. The ratio between the fluacizine concentration in

Laboratory of Psychopharmacology, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR, V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 77, No. 5, pp. 58-61, May, 1974. Original article submitted July 20, 1973.

TABLE 1. Fluacizine Concentrations in the Liver, Brain, and Plasma of Rats after a Single Dose and Prolonged Administration

Object	Concn. of fluacizine (in μg/g or μg/ml) at various times after injection					
	15 min	30 min	1 h	2 h	4 h	6 h
Single intraperitoneal injection						
Liver	62,30 (58,67—65,93)	72,80 (67,09—78,51)	49,50 (46,96—52,04)	30,00 (27,89—32,11)	25,75 (24,57—26,98)	22,50 (20,91—24,09)
Brain	7,90 (7,34—8,46)	12,40 (11,01—13,79)	15,11 (14,55—15,65)	8,13 (7,28—8,98)	6,30 (5,53—7,07)	5,10 (4,37—5,83)
Plasma	2,19 (2,08—2,30)	3,60 (3,34—3,86)	3,21 (2,96—3,46)	1,22 (1,02—1,42)	—	—
Brain / Plasma	3,61	3,44	4,71	6,66	—	—
Intraperitoneal injection for 15 days						
Liver	64,62 (58,39—69,85)	71,30 (65,85—76,75)	47,80 (46,25—49,35)	27,11 (24,48—29,74)	24,80 (22,57—27,03)	23,16 (21,06—25,26)
Brain	11,73 (10,78—12,68)	15,70 (14,03—17,37)	18,10 (16,53—19,67)	12,40 (11,05—13,75)	10,36 (8,79—11,93)	8,90 (8,27—9,53)
Plasma	3,25 (2,82—3,68)	4,60 (4,05—5,15)	3,42 (3,10—3,74)	2,42 (2,11—2,73)	2,24 (1,92—2,56)	1,96 (1,75—2,17)
Brain / Plasma	3,61	3,41	5,29	5,12	4,63	4,54

Legend. Numbers in parentheses denote confidence limits at P = 0.05.

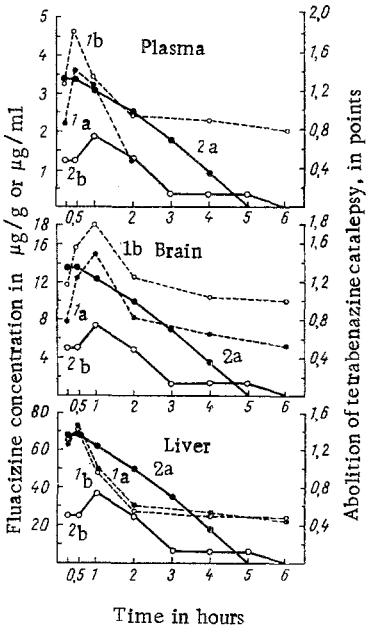

Fig. 1. Comparison of fluacizine concentrations in the plasma, brain, and liver of rats after a single injection and 15 daily intraperitoneal injections of the compounds and its ability to abolish catalepsy induced by tetrabenazine. 1a and 1b) Fluacizine concentrations; 2a and 2b) effect of fluacizine after a single injection and after daily injections for 15 days, respectively. Abscissa, time (in h); ordinate: left) fluacizine concentration (in μg/g or μg/ml), right) abolition of tetrabenazine catalepsy (in points).

the brain and plasma was higher than 1 even after the first dose of fluacizine (Table 1) and it increased at each successive time. This indicates that fluacizine passes readily through the blood-brain barrier. The fluacizine concentration in the liver of the animals 24 h after the first injection was 11 μg/g (8.65-13.35 μg/g).

After administration of fluacizine for 15 days its concentration in the plasma and brain was higher at all times of testing than after a single injection. No statistically significant difference was found in the liver. Meanwhile, 24 h after 14 daily injections of fluacizine, 16.50 μg/g (13.32-19.68 μg/g) of the unchanged compound was determined in the liver. The last (15th) injection of fluacizine was thus given while its concentration in the liver after the previous injections was still high. The ratio between the fluacizine concentrations in the brain and plasma changed only very slightly during prolonged administration, evidently because of maximal saturation and binding of the compound with the plasma proteins and brain structures.

The differences in the manifestation of action of fluacizine during prolonged administration and after a single dose are illustrated in Fig. 1 (curves 2a, 2b). Clearly, the ability of fluacizine to abolish catalepsy in rats induced by tetrabenazine reached a maximum 15 min after a single dose, after which it diminished and the effect finally disappeared 5 h after the injection. Prolonged administration of fluacizine was accompanied by some decrease in its effect and by a shift of the time of the maximum effect to 1 h after the last injection of the compound, although the increase in the total duration of its action was very small.

During prolonged administration of fluacizine, by contrast with a single dose, an increase in the concentration and accumulation of the compound was thus observed in the brain and plasma of the rats (Fig. 1; curves 1a, 1b), a characteristic feature also of chlorpromazine, other related compounds, and the tricyclic antidepressants [3, 4, 11, 15, 18, 19]. No such cumulative effect was observed in the liver. This was

perhaps caused by induction of microsomal enzymes in the liver during prolonged administration of the fluacizine. Chlorpromazine, another member of this series of compounds, has a similar effect in animals and man [6, 7, 12].

When the fluacizine concentrations in the organs and plasma after injection of a single dose were compared with the ability of the compound to abolish catalepsy induced by tetrabenazine, a definite connection was established, especially during the first 3 h after the injection. Later, after administration of the compound its action was reduced, and it ceased completely after 6 h, although its concentration still remained high (Fig. 1). A possible explanation of this phenomenon is that fluacizine, like other phenothiazine derivatives and tricyclic antidepressants [5, 9, 10, 13, 17], is bound intensively with the plasma proteins and tissue structures. This is also confirmed by the fact that 24 h after a single injection and, in particular, after prolonged administration of fluacizine high concentrations of the unchanged compound were determined in the liver. The writers have shown previously that fluacizine is metabolized quickly in rats and that the bulk of the sulfoxylated conversion products of the compound can be demonstrated in the animals' liver during the first hours after injection [1]. It can thus be concluded that the residual quantities of fluacizine in the animals' liver detectable 24 h after administration reflect predominantly the bound form of the compound.

The decrease in the ability of fluacizine to abolish catalepsy after repeated injection, despite its relatively high concentration in the brain and plasma, accords with the corresponding behavior of fluphenazine, promazine, and chlorpromazine with respect to their depression of motor activity [14] and with perazine for its potentiation of hexobarbital sleep [8] in rats. The observed difference in the change in the concentration of the compounds in the brain and the manifestation of their action after a single dose and repeated administration can be explained by several factors. In particular, the higher concentrations of the compound in the plasma and brain after prolonged administration, in the case of total determination of the compound, may reflect an increase in the concentrations chiefly of the bound preparation, and the binding process may combine with induction of the microsomal enzyme of the liver to cause a decrease in the free, active fractions of fluacizine with an accompanying decrease in its effect. At the same time, the possibility of physiological adaptation of the brain structures to the action of fluacizine in the course of its prolonged administration cannot be ruled out.

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