Biochemical Pharmacology, 1962, Vol. 11, pp. 551–556. Pergamon Press Ltd., Printed in Great Britain.

THE METABOLISM OF THIETHYLPERAZINE (TORECAN®)

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(*Received* 24 *January* 1962: *accepted* 1 *February* 1962)

Abstract—The synthesis of thiethylperazine (= Torecan ®) with a ^{35}S-labelled phenothiazine ring is described. Its resorption, distribution in the organism, and its excretion in the faeces, urine and bile are investigated in the rat and compared with similar investigations for thioridazine.

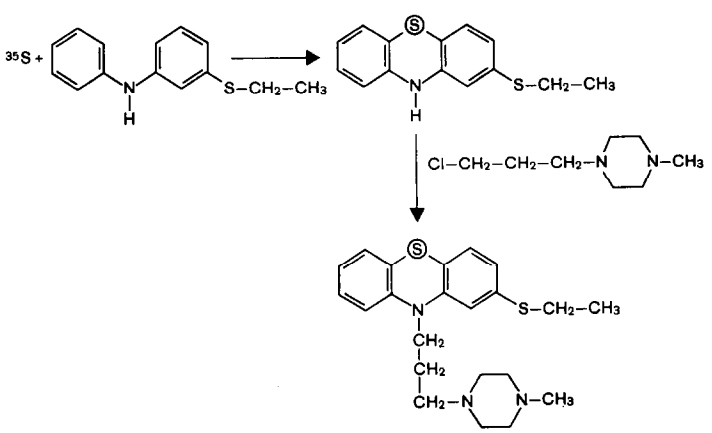
INTRODUCTION

AFTER our studies on the metabolism of thioridazine,[1] we were interested in investigating the metabolism of thiethylperazine, an effective antiemetic. Nothing has so far been mentioned in the literature about the metabolism of similar phenothiazines with piperazine in the side-chain.

MATERIAL AND METHODS

A. Synthesis of ^{35}S-*thiethylperazine*

^{35}S-thiethylperazine (I) was synthesized in a similar way as ^{35}S-thioridazine as shown in the following diagram:



I

1. 3-*Ethylmercapto-phenothiazine*-[9-^{35}S]. A weight of 154 mg (4·8 mM) of radioactive sulphur[1] and 600 mg (2·6 mM) of freshly distilled 3-ethylmercapto-diphenylamine (b.p. 110–115 °C/0·001 mm Hg) were heated at 170 °C for 20 min with 10 mg of iodine in a bulb tube connected to a cold trap. The radioactive hydrogen sulphide formed in the reaction was frozen out with liquid air in the cold trap, then oxidized with iodine solution, acidified with hydrochloric acid and the sulphur recovered in the normal manner. The phenothiazine melt was distilled in a bulb tube. Some sulphur and starting material distilled over up to 140 °C/0·001 mm Hg; the 3-ethylmercapto-phenothiazine-[9-^{35}S] distilled between 140–150 °C/0·001 mm Hg. A total of 90 mg of sublimed radioactive sulphur was recovered from the first runnings and from the oxidation of the hydrogen sulphide formed in the phenothiazine melt.

A second phenothiazine melt was prepared with the radioactive sulphur recovered from the first operation.

The 3-ethylmercapto-phenothiazine-[9-^{35}S] from the two melts was combined and recrystallized from ethyl acetate-cyclo-hexane. A yield of 640 mg (69 per cent based on the sulphur content) of the pure, isomer-free compound (m.p. 95–96 °C) was obtained.

2. ^{35}S-*Thiethylperazine*. A weight of 100 mg (4·3 mM) of sodium was dissolved in 3 ml of absolute methanol, the above 640 mg (2·47 mM) of 3-ethylmercapto-phenothiazine-[^{35}S] in 15 ml of xylene were added and the mixture heated on an oil bath (155 °C) until the xylene began to distill off. A solution of 650 mg (3·67 mM) of freshly distilled 1-methyl-4-(3′-chlor-propyl-1′)-piperazine in 5 ml of absolute xylene was then added and heating continued, moisture being excluded, for 3 hr in the oil bath at 155 °C. The reaction mixture was diluted with ether and extracted with 10% tartaric acid. The aqueous phase was washed with ether and then made alkaline with 30% potassium hydroxide. The base was extracted with ether and after evaporation of the ether distilled in a high vacuum; b.p. 200–210 °C/0·001 mm Hg; yield: 927 mg (93 per cent) as a yellow oil.

Dimaleate. A weight of 927 mg (2·32 mM) of base was dissolved in 10 ml of alcohol and mixed with a concentrated ethanolic solution of 540 mg (4·64 mM) of maleic acid. The salt precipitated out in the form of light yellow massive crystals. Yield: 1365 mg (93 per cent), m.p. 178–179 °C (block, uncorrected, identical with authentic sample).

A thin layer chromatogram on silica gel G "Merck" using ethyl acetate–glacial acetic acid–water (5 : 2 : 2) as the mobile phase gave one blue spot which coincided with the activity peak on spraying with 10% perchloric acid.

The calculated specific activity amounted to approximately 9 mC/mM on 1 March 1961.

B. Determination of radioactivity

The ^{35}S content of the organs and body fluids were determined as described earlier.[1]

C. Tests on metabolism in the rat

Twenty milligrams of ^{35}S-thiethylperazine per kg were administered intravenously or orally in the rats. As the salt was not readily soluble in water, 15 mg of ^{35}S-thiethylperazine dimaleate were dissolved in 1 ml of Solketal* and 2 ml of physiological

* Solketal = 2-dimethyl-4-hydroxymethyl-1,3-dioxolane.

sodium chloride solution then added. The determination of the resorption and the excretion in the bile, faeces and urine, as well as distribution in the organism was carried out as described earlier.[1]

RESULTS AND DISCUSSION

A. Distribution in the organism and resorption

The activities measured in the various organs are again expressed by the factor *F*.[1]

All the organs examined show higher *F*-values and a slower fall off than has been the case for thioridazine and its pyrrolidine analogue ET 758. The blood, liver, bone marrow and lung show *F*-values about twice as high as for ET 758, 1–4 hr after application. Thiethylperazine even reaches a value three times that for thioridazine in the lung. Only the skin and bones show approximately the same behaviour as the other two phenothiazines. Fig. 1 represents the progress of distribution of radioactivity with time

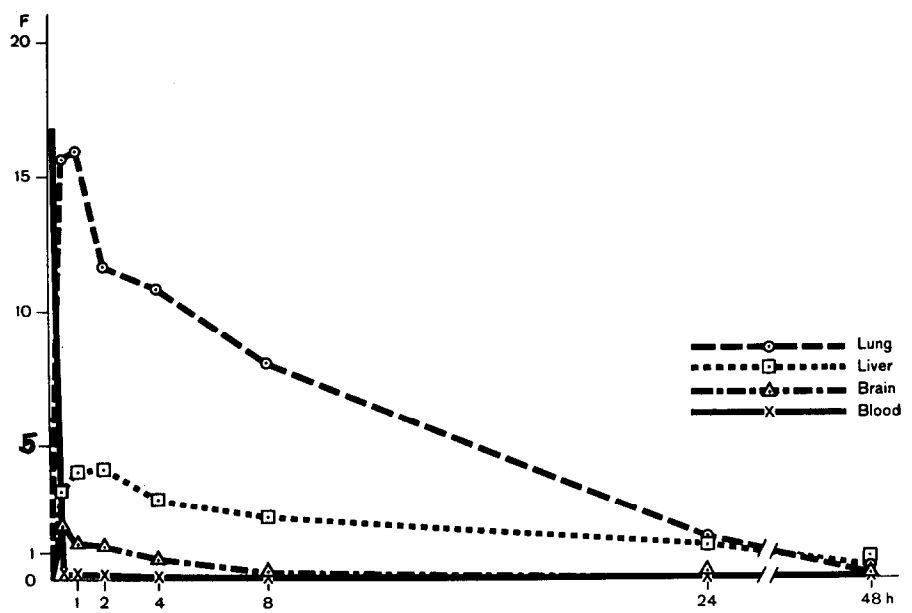


FIG. 1. Distribution of ^{35}S-thiethylperazine in rat organs after intravenous administration

in the lung, liver, brain and blood after intravenous application of ^{35}S-thiethylperazine; analogous curves are shown for the stomach, small intestine and adrenal glands in Fig. 2. The results for the stomach and small intestine show that a substantial amount of the radioactive material is excreted in the stomach. Similar findings have been described, for example, for Preludin.[2]

The resorption of ^{35}S-thiethylperazine proceeds rather more slowly (see Table 1) than that of thioridazine. The wall of the gastrointestinal tract contains less of this phenothiazine than with thioridazine and significantly less than with ET 758. The contents of the lung and liver are likewise smaller than with the derivatives investigated earlier.

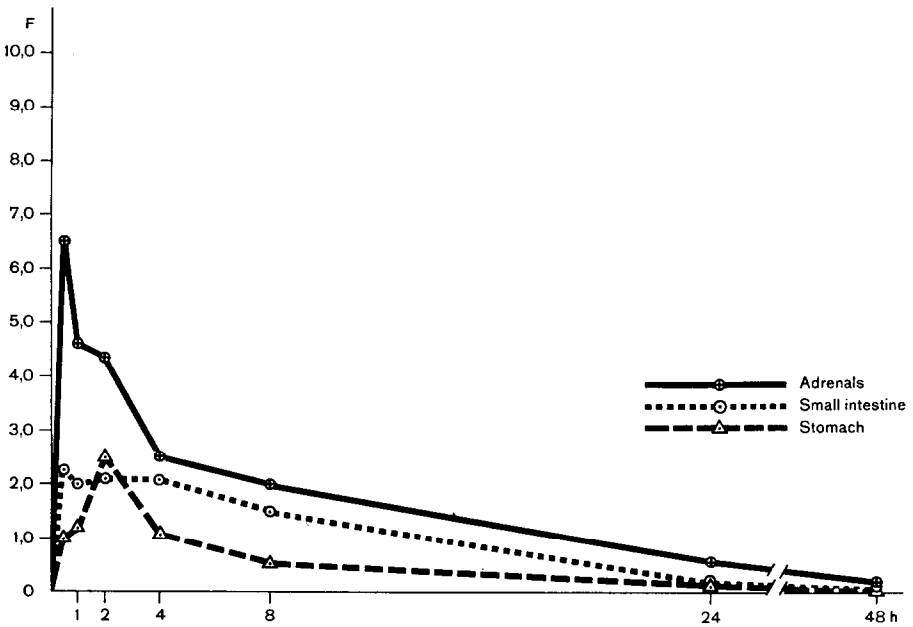


FIG. 2. Distribution of ^{35}S-thiethylperazine in rat organs after intravenous administration

TABLE 1. RADIOACTIVE MATERIAL EXPRESSED AS PER CENT OF THE DOSE OF ^{35}S-THIETHYLPERAZINE ADMINISTERED STILL PRESENT IN THE GASTROINTESTINAL TRACT AFTER RINSING OF THE TRACT WITH 5% TARTARIC ACID (EACH SET OF VALUES GIVES AVERAGES OF RESULTS WITH TWO RATS)

Time (hr)		1	2	4	8	24
Stomach	Content	57	51	30	12	0·07
	Wall	3	2	1	1	0·07
	Content + wall	60	53	31	13	0·14
Intestine	Content	15	20	34	31	8
	Wall	6	6	7	4	1
	Content + wall	21	26	41	35	9
Gastrointestinal Tract Total		81	79	72	48	9
Liver	*F*	0·92	1·26	1·26	1·27	0·56
	%	3·4	5·0	4·9	5·4	2·3
Lung	*F*	0·54	0·68	1·42	1·00	0·13
	%	0·32	0·34	0·94	0·45	0·06

B. Excretion

^{35}S-thiethylperazine is also excreted for the most part in the bile (Fig. 3). This excretion proceeds in a manner almost identical with that of thioridazine and ET 758.

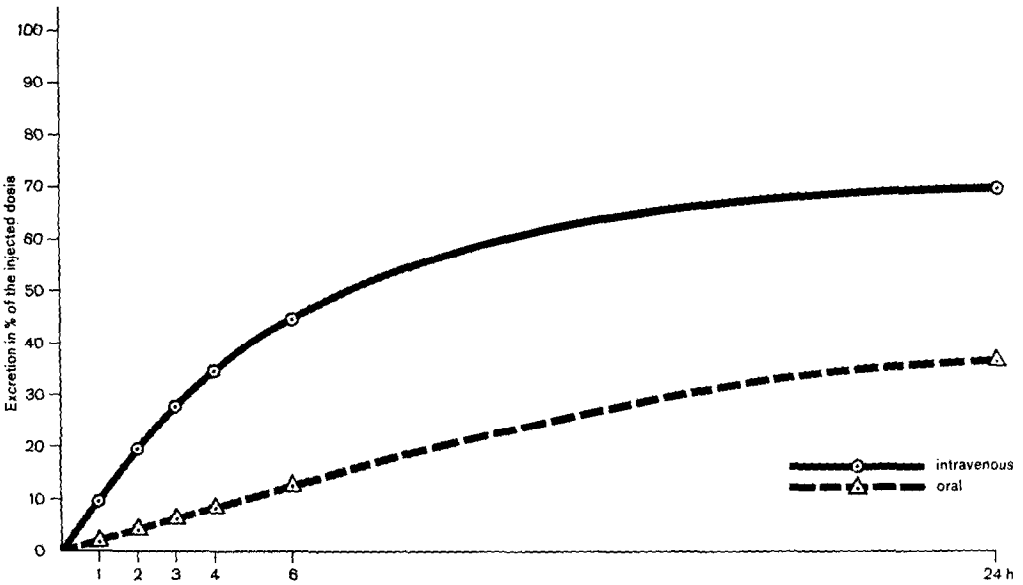


FIG. 3. Biliary excretion of ^{35}S-thiethylperazine by rat

In the intact animal, the majority of the radioactive material appears in the faeces and only a little is excreted in the urine (Table 2).

TABLE 2. EXCRETION OF ^{35}S-THIETHYLPERAZINE METABOLITES IN THE URINE AND FAECES AS PER CENT OF THE ADMINISTERED DOSE

Time	Urine		Faeces	
	after *p.o.*	after i.v.	after *p.o.*	after i.v.
0–2	0·7	0·9	77·0	51·0
2–4		1·3		
4–6	3·1	4·5		
6–8		7·4		
8–24	5·3			
24–48	—	7·9	—	87·1

C. Metabolism

The metabolism of thiethylperazine has not yet been very exhaustively studied. In principle however, metabolites similar to those with thioridazine seem to be formed. A large part of the excreted material again appears in the form of glucuronides in the

bile. This can be shown by paper chromatography before and after incubation with β-glucuronidase of an ethanol extract of freeze-dried rat bile.

REFERENCES

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2. A. ENGELHARDT, D. JERCHEL, H. WEIDMANN and H. WICK, *Arch. exp. Path. Pharmak.* **235**, 10 (1958).