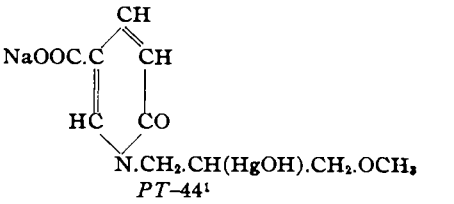
Organic Mercurials: The Influence of Structure on Absorption and Excretion*

By William H. Hunt, Lewis A. Walter and Russel J. Fosbinder

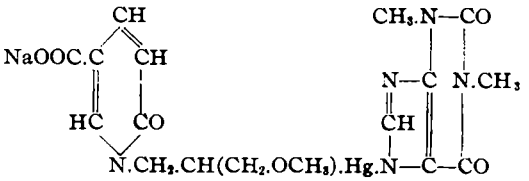
Clinical studies carried out by DeGraff and his co-workers (1) have demonstrated the marked increase in diuretic efficiency resulting from the addition of a xanthine, such as theophylline, to an organic mercurial. From pharmacological studies on Mercurpurin and Salyrgan-Theophylline, they concluded that the superiority of this type of combination was due to two factors, the increased rate and degree of absorption on intramuscular injection and the diminished local reaction occurring at the site of injection.

"Diuretic type" mercurials possess a common structure in that they consist of a cyclic structure containing a solubilizing group and a mercurated side chain joined to the nucleus through an amide linkage. Organic mercury compounds of this type appear to be regularly and rapidly absorbed from the site of injection with little or no retention of mercury by the body. It has been suggested that the absorption and possibly the excretion of these compounds is regulated to a considerable degree by the stability and relative position of the mercury–carbon linkage.

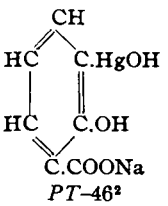
We considered it of interest to study the pharmacologic behavior of two organic mercurials, alone and in combination with theophylline or equivalent weakly acid nitrogen heterocyle. One compound was of the diuretic type, while the other contained mercury directly linked to the carbon atom in the aromatic ring structure. In our investigation, Salyrgan and Salyrgan-Theophylline were employed for purposes of comparison. From the chemical point of view each of the test compounds contained mercury in stable combination, the chief difference being in the position of the mercury–carbon bond. The chemical structure and nomenclature as well as the identification numbers of the compounds investigated are as follows:



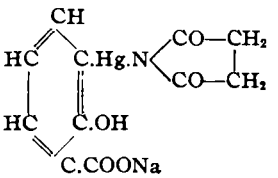
PT–44[1]



PT–44 with Theophylline



PT–46[2]



PT–46 with Succinimide

PT–44, a *N*-(mercurated propyl)-2-pyridone-5-carboxylic acid, was synthesized for study because it is structurally similar to existing diuretic type mercurials. The succinimide complex with *PT*–46 was employed because of the limited solubility of the corresponding theophylline compound.

EXPERIMENTAL

ABSORPTION FROM MUSCLE

In conducting the absorption studies we have made use of the technique described by DeGraff,

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[1] Sodium *N*-(β-hydroxymercuri-γ-methoxypropyl)-2-pyridone-5-carboxylate.

[2] Sodium 3-hydroxymercuri-2-hydroxybenzoate.

TABLE I.—ABSORPTION OF MERCURIALS FROM MUSCLE.

	Time, Hrs.	Time, Min.	Mercury Found, Mg.	Mercury Absorbed, Mean %
PT-44 with theophylline, 9.38 mg. of mercury injected		10	4.02	57.0
		20	3.46	63.1
		40	1.99	78.7
		60	...	...
		80	0.82	89.7
PT-44, 9.38 mg. of mercury injected	2		5.51	41.2
	4		2.80	69.5
	8		2.58	72.5
	16		1.74	81.5
	24		2.62	72.1
	48		1.78	81.2
PT-46 with succinimide, 11.64 mg. of mercury injected		10	5.72	50.8
		20	4.66	60.0
		40	3.92	66.3
		60	...	...
		80	2.11	81.8
PT-46, 11.64 mg. of mercury injected	2		6.98	40.1
	4		5.15	55.6
	8		4.91	57.8
	16		3.78	67.4
	24		3.36	71.1
	48		2.39	79.3
Salyrgan with theophylline,[a] 7.62 mg. of mercury injected		10	3.74	50.9
		20	2.61	67.0
		40	...	...
		60	0.12	96.6
		80	...	...
Salyrgan,[a] 7.62 mg. of mercury injected	2		5.20	31.8
	4		3.98	47.7
	8		2.95	61.3
	16		...	...
	24		1.20	84.3
	48		1.41	80.2

[a] Values obtained from a paper by DeGraff, *et al.* (2).

Batterman and Lehman (2), injecting measured quantities of the solutions into the tibialis anterior muscle of the rabbit. Mercury analyses were performed according to the procedure devised by Winkler (3) which is applicable for the determination of 0.05 to 0.5 mg. of mercury. A total of 71 normal male rabbits was used for this part of the investigation. Some of the values shown in Table I represent the average of 3 to 6 individual determinations. Values for the mean amount of mercury absorbed were obtained by subtracting that found in the muscle from the quantity injected initially.

The results obtained with *PT*-44, *PT*-46 and Salyrgan in combination with a weakly acidic nitrogen heterocyle are in substantial agreement with those reported by DeGraff, *et al.* (2), previously. Over 50% of the injected mercury was absorbed in the first 10 min.; thereafter the rate gradually decreased, but absorption was practically complete after 60 to 80 min.

PT-44, *PT*-46 and Salyrgan were absorbed at a greatly decreased rate, but it will be observed that the rate and degree of absorption did not vary significantly among the three compounds. Considering absorption data alone it would appear to be impossible to distinguish between a diuretic type and an ordinary organic mercurial, and one must conclude that in so far as rate of disappearance from tissue is concerned, the relative position of the mercury in the compound is without effect.

URINARY EXCRETION

Since absorption experiments failed to reveal any significant difference in behavior between the two types of compounds under investigation, it was decided to study the rate of urinary excretion in an attempt to rationalize previous views regarding chemical structure and diuretic action. In this connection Sollman, *et al.* (4), also DeGraff and co-workers (5), have shown clinically and experimentally that Salyrgan produces an intense and fairly immediate excretion of mercury following intramuscular injection, but the rate then declines rapidly due to a decrease in the rate of absorption. The total quantity of mercury voided in the urine of rabbits at varying time intervals following intravenous and intramuscular injection of the compounds was determined. For this purpose a total of 70 normal male rabbits was employed. Tables II and III show the results obtained by both routes of administration.

Referring to Table II, one observes the marked difference in the rate and amount of mercury excreted following the intramuscular injection of *PT*–46 with succinimide as compared to *PT*–44 and Salyrgan with and without theophylline. Less than 20% of *PT*–46 with succinimide was excreted in 72 hrs. While it is evident in the case of Salyrgan that theophylline significantly increased the rate of excretion of mercury, this effect was not so dramatic as the influence on the rate of absorption.

When *PT*–44 with theophylline and *PT*–46 with succinimide were injected intravenously a great difference in the rate of excretion was again noted. Table III shows that while over 50% of the former was excreted in 4 hrs., only 21% of the latter appeared in the urine after 24 hrs.

TABLE II.—EXCRETION OF MERCURY FOLLOWING INTRAMUSCULAR INJECTION

	Time, Hrs.	Mercury Excreted, Mg.	Mercury Excreted, Mean %
PT–44 with theophylline, 9.38 mg. of mercury injected	8	2.92	31.2
	16	3.45	36.9
	24	5.09	54.4
	48	...	...
	72	...	...
PT–44, 9.01 mg. of mercury injected	8	2.08	23.1
	16	3.77	41.9
	24	4.63	51.3
	48	5.85	64.9
	72	...	...
PT–46 with succinimide, 11.64 mg. of mercury injected	8	...	...
	16	...	...
	24	1.093	9.36
	48	...	...
	72	2.216	19.08
Salyrgan with theophylline, 7.92 mg. of mercury injected	8	4.543	57.4
	16	4.006	50.6
	24	5.02	63.38
	48	...	...
	72	...	...
Salyrgan, 7.92 mg. of mercury injected	8	1.49	18.85
	16	2.28	28.85
	24	3.523	44.43
	48	...	...
	72	...	...

TABLE III.—EXCRETION OF MERCURY FOLLOWING INTRAVENOUS INJECTION

	Time, Hrs.	Mercury Excreted, Mg.	Mercury Excreted, Mean %
PT–44 with theophylline, 9.38 mg. of mercury injected	1	2.703	28.81
	4	4.908	52.30
	7	4.962	52.94
	8	...	...
	24	6.828	72.84
	48	6.946	74.10
PT–46 with succinimide, 11.64 mg. of mercury injected	1	...	...
	4	1.77	15.20
	7	...	...
	8	2.62	22.50
	24	2.46	21.15
	48	...	...

TOXICITY

The intravenous toxicity of *PT*–44 with theophylline, *PT*–46 with succinimide and Salyrgan-Theophylline, also the intramuscular toxicity of *PT*–44 and Salyrgan with theophylline, were determined using a series of 92 male New Zealand white rabbits. The values for the acute toxicity, shown in Table IV, represent the equivalent weight of mercury per Kg. of body weight causing death in all animals within 30 min. following intravenous injection and death within 24 hrs. after intramuscular injection.

TABLE IV.—INTRAVENOUS AND INTRAMUSCULAR TOXICITY

Compound	Mg. of Mercury per Kg. of Body Weight: Intravenous	Intramuscular
PT–44 with theophylline	10	60
PT–46 with succinimide	20	..
Salyrgan with theophylline	30	60

It is of interest to consider the difference in toxicity exhibited by *PT*–44 with theophylline and Salyrgan-Theophylline by the intravenous and intramuscular routes. While both compounds appear to be equally toxic by intramuscular administration, the pyridone derivative is three times more toxic than Salyrgan-Theophylline when injected intravenously. This observation was further confirmed by a series of toxicity determinations on the cat.

Although both derivatives are absorbed from muscle at rapid and almost identical rates, as shown previously, the amount of mercury in the blood does not reach the acute fatal level, even though five times the intravenous lethal dose of *PT*–44 with theophylline be administered by this route. Our observations on the relative toxicity of *PT*–44 and Salyrgan with theophylline led us to believe that the fatal effect of these compounds was primarily a direct action on the heart. To confirm this opinion, electrocardiograms from leads I and II were obtained before and after intravenous injection of maximum tolerated doses of each compound, using the rabbit as a test animal. The electrocardiograms showed both compounds exerted immediate but rather transitory toxic effects, characterized in the case of Salyrgan-Theophylline by left axis deviation, inversion of *T*-waves and marked increase in heart rate, while in the case of *PT*–44 with theophylline an exaggerated *T*-wave was apparent with but little change in rate.

DISCUSSION

A comparison of a new diuretic type mercurial, *PT*–44, with Salyrgan has confirmed the observations by DeGraff, *et al.* (2, 5), also Lehman and Dater (6), in respect to the effect of theophylline and related nitrogen heterocycles in enhancing the rate of absorption and excretion of mercury. An

organic mercurial such as *PT*–46, wherein the mercury is directly linked to a carbon atom of the cyclic nucleus, is not unlike a diuretic type compound in so far as absorption is concerned. When excretion studies are considered, the difference in behavior of the two types is marked. Nearly all of the injected mercury, in the case of *PT*–46, is retained and stored in the tissues. This difference cannot be ascribed to a variation in the stability of the mercury–carbon linkage but must be due to specific structural design which permits absorption from the circulation with subsequent metabolic destruction of the compound and retention of mercury.

Organic mercurial diuretics appear to exert a direct and pronounced toxic action on the heart when administered in sublethal and lethal doses. The toxic reaction produced by *PT*–44 with theophylline injected intravenously was much more intense than that caused by Salyrgan-Theophylline although both types of compounds possessed the same margin of safety on intramuscular administration.

SUMMARY

1. The relative position of the mercury–carbon linkage in an organic mercurial does not significantly influence the rate of absorption of the compound from muscle.

2. A weakly acid nitrogen heterocycle, theophylline or succinimide, enhances the rate of absorption of nondiuretic as well as diuretic types of compounds.

3. The type and position of mercury–carbon linkage exerts a profound influence on the retention of mercury whether it be administered intravenously or intramuscularly since a nondiuretic type is almost completely retained.

4. Succinimide coupled with a nondiuretic type of derivative does not significantly alter the degree of excretion of mercury.

5. Chemical stability of the mercury–carbon linkage appears to be of secondary importance in so far as absorption and excretion are concerned.

6. An organic mercurial derived from 2-pyridone-5-carboxylic acid was found to be more toxic than Salyrgan.

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Bacteriostatic Properties of Certain Derivatives of Thiophene*

By H. W. Rhodehamel, Jr., and E. F. Degering

The chemical and physical properties of thiophene and its derivatives have been studied extensively by many investigators since its discovery by Victor Meyer in 1883 (1). No systematic study has been made, however, of the bacteriostatic properties of thiophene or its derivatives, although a few thiophene compounds have been used in medicine. Thiophene itself has been used as an antiseptic (2), sodium thiophenesulfonate and diiodothiophene have been used in the treatment of skin diseases (3), and tetrabromothiophene has been recommended as an efficient antiseptic (4). Many investigators believe that the large percentage of thiophene derivatives in ichthyol is responsible for its therapeutic properties (5, 6).

Recently a patent was issued in which it was claimed that aromatic mercury substituted derivatives of thiophene "have extraordinarily high potency as antiseptics and germicides and at the same time are characterized by relatively low toxicity and other desirable properties (7)." Several studies have shown that the replacement of a

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