THE COMPARATIVE TOXICITY OF A NEW MERCURIAL—MERCUROSAL.*

(DI-SODIUM-HYDROXYMERCURI-SALICYL-ACETATE, $C_6H_3\begin{cases}COONa\\OCH_2COONa\\HgOH\end{cases}$)

BY L. W. ROWE.

The exhibition of mercury in some form is now an important part of the standard treatment of syphilis. Because of the toxic action of ordinary mercury salts upon protoplasm other than that of the *Spirochaeta pallida*, much research has been conducted in an effort to discover a compound of mercury which would be relatively low in toxicity but effective as an anti-syphilitic agent. Comparative tests which have been made upon a new mercury compound, mercurosal (di-sodium-hydroxymercuri-salicyl-acetate, $C_6H_3\begin{cases}COONa\\OCH_2COONa\\HgOH\end{cases}$), and which are given in detail later in this article, have seemed to prove that it is relatively less toxic than other mercury salts. Clinical tests in great number have thoroughly demonstrated its efficiency in the actual treatment of syphilitic patients.

Many articles concerning the relative toxicity of mercurial compounds have been published but the recent work of Schamberg, Kolmer and Raiziss[1] is so comprehensive as to make it unnecessary to give a thorough summary of the literature at this time. Briefly, their article gives experiments demonstrating the comparative toxicity to white rats and rabbits of the mercurials which were being used prior to 1915. Their most important conclusion appeared to be that all mercury compounds known at that time were equally toxic in proportion to the amount of mercury each contained.

The toxicity of mercury compounds is difficult to determine definitely because of the fact that animals vary considerably in the degree of their resistance. The action of mercury being cumulative, the determination of the minimum lethal dose is dependent upon two variables, namely, the rate of absorption and the rate of elimination. Most of the experimental work reported below has been carried out with the idea of overcoming one variable by administering the mercury solutions intravenously. The data gathered using the immediate lethal dose method seems at first glance to have obviated both of the difficulties mentioned above but another factor is introduced, the degree of shock, which is not entirely uniform in different animals of the same species no matter how carefully the animals may be selected.

In the following tables of data opportunity is afforded for the comparison of the toxicities of different compounds of mercury upon the same animal using different methods of administration and also upon a variety of animals.

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* Scientific Section, A. Ph. A., Cleveland meeting, 1922.

[1] *Journal of Cutaneous Diseases*, 33, 819, 1915.

TABLE I.

Toxicity to Guinea Pigs. Subcutaneous Administration.

Mercuric chloride. Wt., Gm.	Dose, Gm. per Kg.	Hg 74%. Died after days.
440	0.004	0
500	0.005	0
530	0.005	4
440	0.005	0
475	0.006	0
430	0.006	0
480	0.006	0
360	0.007	0
390	0.007	4
327	0.007	0
540	0.008*	2
440	0.008*	3

Mercury succinimide. Wt., Gm.	Dose, Gm. per Kg.	Hg 51%. Died after days.
461	0.005	0
449	0.010	0
507	0.011	0
462	0.012*	3
429	0.012*	3
439	0.014	4
400	0.016	3
497	0.018	2
457	0.020	2

Mercurosal. Wt. Gm.	Dose, Gm. per Kg.	Hg 44%. Died after days.
680	0.068	0
593	0.068	0
540	0.090*	4
481	0.090*	6
580	0.113	3
476	0.113	5

Mercuric iodide red. Hg 44%.

0.010 to 0.015* Gm. per Kg. = M. l. d. Detailed data not available.

Anhydride of mercury.		Salicylic acid.
420	0.005	0
340	0.005	0
370	0.006*	2
480	0.006*	2
320	0.006*	1
480	0.007	2
500	0.007	1

0 Animals thus designated did not die during period of observation.

* Dose found to be the m. l. d.

Dose is in grams per kilogram body weight throughout the tables.

TABLE II.

Toxicity to Guinea Pigs. Intravenous Administration.

Mercuric chloride. Wt., Gm.	Dose, Gm. per Kg.	Hg 74%. Died after days.
318	0.0010	0
395	0.0015	0
368	0.0015	0
327	0.0015	0
358	0.0020*	2
360	0.0020*	2
286	0.0020*	0
252	0.0025	2
286	0.0025	3
451	0.003	2
446	0.004	1
572	0.005	1
495	0.006	1

Mercuric iodide. Wt.	Dose.	Hg 44%. Died after days.
344	0.0015	0
350	0.0020	0
327	0.0025	0
477	0.004	1
477	0.004	1
350	0.003*	7
290	0.003*	6
320	0.003*	1
395	0.0050	1
375	0.008	1

Mercurosal. Wt.	Dose.	Hg 44%. Died after days.
427	0.010	0
405	0.015	0
419	0.015	0
359	0.015	0
393	0.020*	0
384	0.020*	1
349	0.020*	2
336	0.025	2

Mercury salicylate. Wt.	Dose.	Hg 58%. Died after days.
405	0.00	0
414	0.0025	0
355	0.0025	0
373	0.0025	8
366	0.003*	3
425	0.003*	4
434	0.004	3
427	0.004	2

0 designates animals which lived during period of observation.

* The m. l. d. found.

TABLE III.

Toxicity to Rabbits. Intravenous Administration.

Mercuric iodide red		Hg 44%.	Mercury salicylate.		Hg 58%.	Mercurosal.		Hg 44%.
Wt., Gm.	Dose, Gm. per Kg.	Died after days.	Wt.	Dose.	Died after days.	Wt.	Dose.	Died after days.
2000	0.005	0	2300	0.002	0	2180	0.005	0
2800	0.004	0	3120	0.003	0	2420	0.010	0
1783	0.006*	7	2320	0.004	0	2020	0.015*	0
3150	0.008	7	2240	0.005*	14	2340	0.015*	1
1620	0.010	1				2360	0.018	1
						2500	0.020	1
						2270	0.021	1

0 Designates animals which lived during the period of observation.

* M. l. d. found.

TABLE IV.

Toxicity to Dogs. Intravenous Administration.

Mercuric chloride.		Hg 74%.	Mercuric iodide red.		Hg 44%.	Mercurosal.		Hg 44%.
Wt., Kg.	Dose.	Died after days.	Wt., Kg.	Dose.	Died after days.	Wt.	Dose.	Died after days.
9	0.0036	0	11.0	0.0025	0	8.0	0.020	0
9	0.0040	0	10.5	0.0030	0	20.3	0.015	0
13	0.00037	3	9.0	0.0035	0	11.5	0.020	0
8	0.0041	3	9.0	0.0040*	5	8.0	0.020	0
10	0.0050	6	7.0	0.0040*	3	13.6	0.025*	1
7	0.0060	3	9.5	0.0050	5	6.0	0.025*	1
9	0.007	4	7.5	0.0080	2	6.0	0.027	1
6	0.008	1	6.5	0.0100	1	6.0	0.033	1

M. l. d. is about 0.0040 Gm. per Kg.

0 designates animals which did not die during period of observation.

* M. l. d. found.

TABLE V.

Comparison of Immediate Lethal Doses. Rabbits. Intravenously.

Mercuric chloride.	Hg 74%.	Mercurosal.	Hg 44%.	Test of mercurosal upon dogs.	
Wt., Kg.	Dose, Gm. per Kg.	Wt.	Dose, Gm. per Kg.	Wt., Kg.	Dose, Gm. per Kg.
3.42	0.00731	1.9	0.0263	4.3	0.0256
3.10	0.00887	2.1	0.0247	8.1	0.0222
2.66	0.00752	1.94	0.0227	13.8	0.0246
		3.35	0.0298	19.6	0.0234
Average is 0.0079 or 0.008 Gm. per Kg.		Average of four is 0.0259 or 0.026 Gm. per Kg.		Average is 0.024 Gm. per Kg.	

TABLE VI.

Summary of Results.

Hg compound.	Hg content, per cent.	Animal.	Dose, Gm. per Kg.	Administered.
Mercurosal	44	Guinea pig	0.09	Subcutaneously
Mercurosal	44	Guinea pig	0.020	Intravenously
Mercurosal	44	Rabbit	0.015	Intravenously
Mercurosal	44	Dog	0.025	Intravenously
Mercurosal	44	Rabbit	0.026	Immediate lethal dose
Mercuric chloride	74	Guinea pig	0.008	Subcutaneously
Mercuric chloride	74	Guinea pig	0.0020	Intravenously
Mercuric chloride	74	Dog	0.0040	Intravenously
Mercuric chloride	74	Rabbit	0.0080	Immediate lethal dose
Mercuric iodide red	44	Guinea pig	0.015	Subcutaneously

Mercuric iodide red	44	Guinea pig	0.003	Intravenously
Mercuric iodide red	44	Rabbit	0.006	Intravenously
Mercuric iodide red	44	Dog	0.004	Intravenously
Mercury salicylate	58	Guinea pig	0.003	Intravenously
Mercury salicylate	58	Rabbit	0.005	Intravenously
Mercury succinimide	51	Guinea pig	0.012	Subcutaneously

TABLE VII.

Toxicity Ratios.

Mercurosal to	As salts.	Same Hg content.	Animal.	Administered.
Bichloride	1 to 11.25	1 to 6.7	Guinea pig	Subcutaneously
Bichloride	1 to 10.0	1 to 6.0	Guinea pig	Intravenously
Bichloride	1 to 6.25	1 to 3.7	Dog	Intravenously
Bichloride	1 to 3.25	1 to 2.0	Rabbit	Immediate lethal dose
Mercuric iodide	1 to 6.0	1 to 6.0	Guinea pig	Subcutaneously
Mercuric iodide	1 to 6.7	1 to 6.7	Guinea pig	Intravenously
Mercuric iodide	1 to 2.5	1 to 2.5	Rabbit	Intravenously
Mercuric iodide	1 to 6.25	1 to 6.25	Dog	Intravenously
Mercury salicylate	1 to 6.7	1 to 5.1	Guinea pig	Intravenously
Mercury salicylate	1 to 3.0	1 to 2.27	Rabbit	Intravenously
Mercury succinimide	1 to 7.5	1 to 6.4	Guinea pig	Subcutaneously

DISCUSSION OF RESULTS.

In the tables presented the toxicity of some of the most common compounds of mercury is compared directly with the toxicity of mercurosal. In testing mercury salicylate the solution was made with piperazine in accordance with Schamberg's suggestion as a strong solution of piperazine was found to be practically non-toxic when injected intravenously.

Taking into consideration the difference in percentage of mercury of the various compounds the average ratio shows mercurosal to be but one-fifth as toxic as either the bichloride, iodide, salicylate or succinimide. If the results upon rabbits are disregarded the average ratio is one to six.

The data prove that mercurosal is a compound of mercury which is relatively low in toxicity. It does not, therefore, fall into the class of "numerous organic combinations" of mercury referred to by Schamberg in the fourth conclusion of his extensive article which says, "The inorganic salts, as represented by the bichloride of mercury, are no more toxic than the numerous organic combinations that are commonly employed."

The margin of safety of the therapeutic dose of mercurosal can best be realized when it is considered that the ultimate intravenous toxic dose to an average-sized dog of 10 Kg. is not less than 0.20 Gm., while an average-sized human being will weigh seven times as much and receive only 0.10 Gm. intravenously making a margin of about fourteen times.

When employed intravenously mercurosal has no appreciable effect upon the wall of the vein near the site of injection. This was proved by a long series of intravenous injections made into the same dog at practically the same point on the vein. In this respect it differs from other mercurials, particularly the bichloride.

In order to safeguard the patient and also the physician, the toxicity of every mercurial which is used intravenously as an antisyphilitic agent should be controlled by a physiological test such as the determination of the immediate lethal

dose to rabbits. Such a control is maintained over mercurosal and is practically as necessary as the present government supervision of the manufactured lots of the arsenical compounds, arsphenamine and neo-arsphenamine.

Data relative to elimination, tolerance, and effect upon the kidney will probably be presented in another article.

In order to show that mercurosal is not affected by contact with alcohol (pure or denatured), ether or aldehydes, an experiment was conducted in which small portions of the same lot were treated for several hours with warm 95% alcohol, warm denatured alcohol, ether, and alcohol containing a large amount of aldehydes, respectively. The control and treated portions were tested for immediate toxic action upon rabbits and the average of several tests of 2% solutions of each was as follows:

Sample.	Immediate lethal dose.
Control	0.0271 Gm. per Kg.
Treated with denatured alcohol	0.0323 Gm. per Kg.
Treated with pure 95% alcohol	0.0348 Gm. per Kg.
Treated with aldehyde	0.0324 Gm. per Kg.
Treated with ether	0.0360 Gm. per Kg.

The results of this experiment are not as consistent as might be desired but considering the limit of error of a physiological test agree well enough to indicate that there was very little difference in toxic action in the samples and particularly that the treated portions were not more toxic than a portion of the same lot which was not treated experimentally.

CONCLUSIONS.

1. The toxicity of mercurosal is not affected by contact with alcohol, ether or aldehydes.

2. The wall of the vein is not injured by repeated intravenous injections of 2% solutions of mercurosal.

3. Mercurosal is approximately one-fifth as toxic as some other salts of mercury such as the bichloride, iodide, salicylate or succinimide even when equivalent mercury content is considered.

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A NEW ASPECT OF THE TOXICOLOGY OF ARSENIC.*

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This report deals with the toxicology of white arsenic (arsenic trioxide U. S. P. or arsenious oxide), and places a newly recognized responsibility upon the prescriber, the manufacturer and the dispenser of this substance in the undissolved form. Although it is customary to administer arsenic trioxide dissolved, it is at times prescribed undissolved, in which state the potency varies to a marked degree,

* Read before Scientific Section, A. Ph. A., Cleveland meeting, 1922.

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