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Solustibosan and Ureastibamine in Treatment of Kala-Azar in Chinese Hamsters.

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In a previous communication[1] it was demonstrated that Chinese hamsters infected with *Leishmania donovani* can be cured of the infection by neostibosan.

This report deals with chemotherapeutic tests with solustibosan and ureastibamine in Chinese hamsters with especial reference to their relative toxicity and curative value in comparison with neostibosan. Ureastibamine is known to be highly potent as well as highly toxic in the treatment of human kala-azar,[2] while solustibosan, a liquid preparation, which has the advantage of being administered intramuscularly, has been claimed to possess curative value and great tolerability in experimental and human kala-azar.[3]

Experiment I. Determination of the *maximum non-lethal dose* and *universal lethal* dose of solustibosan and ureastibamine in normal Chinese hamsters. The definition of doses and the experimental procedures, as described in a previous communication[4] were followed, with the exception that for each test dose a group of 10, instead of 20 animals was used. Ureastibamine was freshly prepared each time in a 5% sterile aqueous solution, and given subcutaneously. Solustibosan was used undiluted and also given subcutaneously. The results of the test doses are given in Tables I and II.

TABLE I.
Mortality Rate of Hamsters to Test Doses of Solustibosan.

Dose, cc per kilo	No. of hamsters	No. of deaths	Mortality %
20	10	0	0
30	10	0	0
40	10	2	20
80	10	4	40
100	10	4	40
120	10	9	90
140	10	10	100

From these tables it is evident that for solustibosan 30 cc per kilo is the *maximum non-lethal dose* and 140 cc per kilo, the *universal*

1 Wang, C. W., and Lee, C. U., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 674.
2 Lee, C. U., and Chu, C. F., *Chinese Med. J.*, 1935, **49**, 328.
3 Kikuth, W., and Schmidt, H., *Arch. Schiffs. u. Tropen-Hyg.*, 1938, **42**, 189.
4 Wang, C. W., and Lee, C. U., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 670.

TABLE II.
Mortality Rate of Hamsters to Test Doses of Ureastibamine.

Dose, g per kilo	No. of hamsters	No. of deaths	Mortality %
0.5	10	0	0
1.0	10	2	20
2.0	10	5	50
3.0	10	10	100

lethal dose; and for ureastibamine 0.5 g and 3.0 g per kilo respectively. As the expression of the units of doses for solustibosan, ureastibamine and neostibosan was not the same the comparison between the different doses could only be made with their respective antimony contents. It is known that 1 cc of solustibosan contains 20 mg of Sb; 100 mg of neostibosan, 42 mg of Sb; and 100 mg of ureastibamine, 35 mg of Sb. The value of the antimony content in ureastibamine was based on Brahmarchari's determination, but it has been found to vary from 20 to 43% in different samples.[5] In Table III the different doses with their antimony equivalents are given, and the doses for neostibosan were taken from a previous work.[4]

TABLE III.
Antimony Equivalents in *Maximum Non-lethal Dose* and *Universal Lethal Dose* of Solustibosan, Neostibosan, and Ureastibamine in Normal Hamsters.

	Maximum non-lethal dose			Universal lethal dose		
	cc per kilo	g per kilo	mg Sb per kilo	cc per kilo	g per kilo	mg Sb per kilo
Solustibosan	30		600	140		2800
Neostibosan		1	420		4	1680
Ureastibamine		0.5	175		3	1050

From Table III it is obvious that the antimony contents of the *maximum non-lethal dose* and *universal lethal dose* are highest in solustibosan and lowest in ureastibamine. This indicates that hamsters can tolerate much more antimony in the form of solustibosan than in the form of either neostibosan or ureastibamine. In other words, among the 3 antimony compounds tested, solustibosan is least and ureastibamine most toxic for normal hamsters.

Experiment II. The relative curative value of solustibosan, neostibosan, and ureastibamine in infected Chinese hamsters. Sixty infected hamsters were equally divided into 3 groups, each consisting of 20 hamsters. Each group was treated exclusively with one drug.

[5] Ghosh, S., Chopra, R. N., and Chatterjee, N. R., *Ind. J. Med. Res.*, 1928, **16**, 461.

Treatment was started 77 days after the infection with kala-azar. Neostibosan was freshly prepared each time in a 1% sterile aqueous solution and ureastibamine in a 0.5% solution. A constant dose of 400 mg per kilo for neostibosan and 200 mg per kilo for ureastibamine was given 3 times a week subcutaneously. Solustibosan was given undiluted and also subcutaneously. A constant dose of 8 cc per kilo was given in the same frequency as the other 2, until a total of 120 cc per kilo was reached, when a constant dose of 16 cc per kilo was maintained. One to 4 hamsters were killed from time to time during the course of treatment and smears of spleen, liver and bone marrow were examined for parasites. The results are given in Table IV in which only the parasitological findings of spleen smears were recorded, as they were found to be most conclusive.

TABLE IV.

Relative Value of Solustibosan, Neostibosan, and Ureastibamine in Experimental Kala-azar in Chinese Hamsters.

Total dose per kilo in			No. hamsters killed and examined	Leishman-donovan bodies in spleen		Mortality during treatment, %
cc	g	mg Sb		No. positive hamsters	No. negative hamsters	
			Solustibosan			
24		480	4	4	0	
48		960	2*	2	0	
72		1440	2	2	0	
96		1920	4	4	0	
120		2400	3	2	1	10
152		3040	3	0	3	
200		4000	2	0	2	
			Neostibosan			
	1.2	504	4	4	0	
	2.4	1008	2	2	0	
	3.6	1512	2	0	2	
	4.8	2016	2	1	1	30
	6.0	2520	2	0	2	
	7.6	3192	2	0	2	
			Ureastibamine			
	1.2	420	4	4	0	
	2.2	770	3	2	1	60
	2.6	910	1	0	1	

*These two hamsters only received liver puncture and the treatment in them was continued.

In Table IV it is shown that negative spleen smears in the treated hamsters began to appear after a total of 120 cc or 2400 mg Sb per kilo in the form of solustibosan, 3.6 g or 1512 mg Sb per kilo in the form of neostibosan and only 2.2 g or 770 mg Sb per kilo in the form of ureastibamine. It is obvious that much more antimony in the form of solustibosan is required to give the same curative effect as

with either neostibosan or ureastibamine. In terms of their antimony contents neostibosan is certainly a more effective drug than solustibosan, but inferior to ureastibamine in infected hamsters (the same conclusion is true when neostibosan and ureastibamine are compared by weight).

The mortality rate during the course of treatment was highest in the group of hamsters treated with ureastibamine, and lowest with solustibosan. The high mortality rate with ureastibamine probably can partly be explained by the occurrence of extensive ulceration and infection at the site of injection, as a result of improper administration of the drug by subcutaneous route, and as the intravenous injections in hamsters can not be carried out (solustibosan, however, gave practically no local reaction to hamsters). Nevertheless, the difference of mortality rate between solustibosan and neostibosan and between neostibosan and ureastibamine is not statistically significant.

Summary and Conclusions. The *maximum non-lethal dose* and *universal lethal dose* of solustibosan and ureastibamine in normal Chinese hamsters were determined and their values were compared with those neostibosan. In terms of their antimony contents hamsters tolerated much more antimony in the form of solustibosan than in the form of either neostibosan or ureastibamine. Evidently solustibosan is least, while ureastibamine is most toxic among the 3 antimony compounds for normal hamsters.

In the infected hamsters much more antimony in the form of solustibosan than that in the form of either neostibosan or ureastibamine was required to bring about a cure. It is obvious that ureastibamine is the most and solustibosan the least potent drug in the treatment of infected hamsters. The mortality rate during the course of treatment was highest with ureastibamine and lowest with solustibosan, but the differences are not statistically significant.