10601

Solustibosan in Treatment of Kala-Azar in Chinese Hamsters.

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In the treatment of kala-azar in Chinese hamsters it was shown[1] that with 3 injections a week more antimony in the form of solustibosan than that in the form of neostibosan was required to bring about a cure. Recently, however, Kikuth and Schmidt,[2,3] working on the same problem with European hamsters, reported that by increasing from bi-weekly to daily injections, 135 mg of Sb in the form of solustibosan gave the same curative effect as 210 mg of Sb in the form of neostibosan. Hence, they concluded that the former is superior to the latter. Our observations do not, however, seem to agree with theirs, and therefore are here reported.

The present study was carried out at 2 different periods with 2 lots of infected hamsters. Lot A consisted of 28 and Lot B of 20 infected hamsters. The course of treatment in the latter lot was started about 2 months after that in the former lot was concluded. The infective dose of *Leishmania donovani* suspension was the same for all hamsters in each lot and was inoculated intraperitoneally. The presence of infection in the hamsters was proven by liver puncture. Forty-eight infected hamsters were equally divided into 2 groups, each consisting of 14 from Lot A and 10 from Lot B. One group was treated with solustibosan and the other with neostibosan. The duration of infection in the hamsters before the commencement of treatment was 31 days in Lot A and 49 days in Lot B. Neostibosan was freshly prepared each time in a 1% sterile aqueous solution and solustibosan was given undiluted. When an ampoule of the latter drug was not entirely used, it was kept under sterile condition in an ice-chest for use on the ensuing day. A constant daily dose of 6 cc (120 mg Sb) per kilo for solustibosan, and 400 mg (168 mg Sb) per kilo for neostibosan was given subcutaneously. The antimony content in the daily doses of solustibosan and neostibosan was comparable to that used by Kikuth and Schmidt. In Lot A, 2 to 4 hamsters were killed one week* after the completion of a series of 10, 15, 20 and

1 Wang, C. W., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 418.

2 Kikuth, W., and Schmidt, H., *Arch. Schiffs. u. Tropen-Hyg.*, 1938, **42**, 189.

3 Quoted by Schmidt, H., and Peter, F. M., *Advances in the Therapeutics of Antimony*, Georg Thieme, Leipzig, 1938, 206.

* In a previous study,[1] the hamsters were also killed one week after the completion of treatment.

TABLE I.

Relative Value of Daily Injections of Solustibosan and Neostibosan in Experimental Kala-azar in Chinese Hamsters.

Lot of hamsters	Hamster No.	Total No. daily injections	Total dose per Kg in cc	g	mgSb	Leishman-Donovan bodies in spleen: smear	section	Mortality during treatment, %
			Solustibosan.					
A.	2352	10	60		1200	+	++	
	2353	10	60		1200	0	0	
	2354	10	60		1200	++	+++	
	2355	15	90		1800	++	++	
	2356	15	90		1800	++	+++	
	2357	died after 12 injections						
	2358	15	90		1800	++	+++	
	2359	20	120		2400	(+)	(+)	
	2360	20	120		2400	+	+	
	2361	20	120		2400	+	++	
	2362	25	150		3000	++	++	
	2363	25	150		3000	+	++	12.5
	2364	25	150		3000	0	(+)	
	2365	25	150		3000	+	++	
B.	2562	25	150		3000	++	++	
	2565	died after 25 injections						
	2566	25	150		3000	+++	+++	
	2567	25	150		3000	0	0	
	2568	25	150		3000	(+)	+	
	2570	25	150		3000	++	++	
	2571	25	150		3000	+++	+++	
	2572	25	150		3000	(+)	(+)	
	2573	25	150		3000	0	0	
	2574	died after 25 injections						
			Neostibosan.					
A.	2366	died after 4 injections						
	2367	10		4	1680	(+)	(+)	
	2368	died after 9 injections						
	2369	10		4	1680	0	0	
	2370	10		4	1680	(+)	(+)	
	2371	15		6	2520	0	0	
	2372	15		6	2520	(+)	(+)	
	2373	died after 15 injections						
	2374	20		8	3360	0	(+)	
	2375	20		8	3360	(+)	(+)	
	2377	20		8	3360	0	0	
	2378	25		10	4200	0	0	
	2379	25		10	4200	0	0	
	2380	25		10	4200	+	+	
B.	2548	died after 23 injections						25.0
	2550	died after 25 injections						
	2551	25		10	4200	+	(+)	
	2552	25		10	4200	(+)	(+)	
	2553	25		10	4200	0	0	
	2554	25		10	4200	++	++	
	2555	25		10	4200	0	0	
	2556	25		10	4200	+	+	
	2557	25		10	4200	0	0	
	2558	died after 25 injections						

0 = Not found.
(+) = Very few found.
+ = Found in every 10-20 oil immersion fields.
++ = " " " 5-10 " " "
+++ = " " " 1-5 " " "

25 daily injections; while in Lot B all the hamsters were killed one week after the completion of a series of 25 daily injections. Smears and sections were made from the spleen and examined for parasites. The results of the treatment of Lot B were combined with those of Lot A.

As shown in Table I, in the group of hamsters treated with solustibosan, all except 3 animals still showed a large number of parasites in the sections made from the spleen. On the other hand, in the group treated with neostibosan, 8 hamsters showed no parasites in the sections of the spleen, while the rest showed in most instances only a few parasites. It appears obvious that solustibosan given at the daily dose of 120 mg of Sb for 10 to 25 consecutive days showed a lower rate of cure than neostibosan given at the daily dose of 168 mg of Sb for the same length of time, although the difference was not statistically significant. Further study on a large series of animals for each group might elucidate this point.

Another point of interest which has been brought out from the present study was that for a given total number of injections or a given total dose of antimony in the form of either solustibosan or neostibosan, daily injections appeared to be less effective than bi-weekly or tri-weekly injections. Table II illustrates this point. The data on bi-weekly or tri-weekly injections are those of 2 previous studies[1, 4] and some unpublished observations. It is evident that with increasing frequency of injections there is a decreased rate of apparent cure. The criterion of an apparent cure, as described previously,[4] consists of either a negative spleen smear at autopsy or a negative liver puncture smear as well as a negative spleen puncture smear. With bi-weekly injections, neostibosan has been shown to give an apparent cure-rate nearly twice as high as with daily injections, and the dif-

TABLE II.
Relative Value of Daily, Bi-weekly, and Tri-weekly Injections of Solustibosan and Neostibosan in Experimental Kala-azar in Chinese Hamsters.

	Solustibosan		Neostibosan		
Frequency of injections	Daily	Tri-weekly	Daily	Tri-weekly	Bi-weekly
Dose in mgSb per Kg	120	160-320	168	168	84-378
Total dose in mgSb per Kg	1200-3000	1440-3040	1680-4200	1512-4032	2100-4200
No. of hamsters killed and examined	21	12	18	12	*36
No. of hamsters showing negative spleen smears	4	4	9	10	34
Rate of apparent cure %	19.0	33.3	50.0	83.3	94.4

*Twenty-one of these 36 hamsters were not killed but all showed negative liver and spleen punctures 3 weeks after the completion of treatment.

[4] Wang, C. W., and Lee, C. U., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 674.

ference of apparent cure-rate between bi-weekly and daily injections was found to be statistically significant (44.4 ± 12.5).[5] It appears likely that the decreased effectiveness of neostibosan and solustibosan following daily injections is related to the increased rate of excretion of antimony. Brahmachari[6] has shown that with repeated injections the amount of antimony excreted by the kidneys was fairly proportional to the amount of antimony present in the tissues, and that when the amount of antimony present in the tissues reached a maximum concentration, its excretion suddenly became increased out of proportion to the amount present in the tissues. With daily injections it seems likely that the amount of antimony present in the tissues reaches a state of maximum concentration rather early; otherwise, the cumulative effect of antimony would have manifested itself.

The higher mortality rate in the group of hamsters treated with neostibosan agrees with our previous experience, although the difference may not be significant.

Conclusions. In the treatment of kala-azar in Chinese hamsters it was found that with daily injections of the drugs under investigation, less antimony in the form of solustibosan than that in the form of neostibosan did not produce the same curative effect, as has been claimed by Kikuth and Schmidt, *i. e.*, the curative effect of solustibosan did not increase with the increase of the frequency of injections. 2. Daily injections of either solustibosan or neostibosan appear to be less effective than bi-weekly or tri-weekly injections.

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10602

Sensitizing Capacity of Polysaccharide of *Monilia tropicalis.*

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Active sensitization of guinea pigs has been generally successful with gram-positive bacteria but not with gram-negative ones. Yet under suitable methods of preparation polysaccharides derived from some of the latter microörganisms are capable of inducing a state of

[5] Fortuyn, A. B. D., *China Med. J.*, 1929, **43**, 31.

[6] Brahmachari, U. N., and Sen, P. B., *Ind. J. Med. Res.*, 1924, **12**, 113.