TREATMENT OF LEWISITE SHOCK WITH SODIUM SALT SOLUTIONS

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Lewisite poisoning in animals presents a picture of initial haemoconcentration, due to plasma loss to the soft tissues, followed by a haemolytic anaemia (Cameron and Courtice: awaiting publication). The early picture is indistinguishable from that of shock due to other causes and, as it is readily produced and its severity easily controlled, we have used this method in preliminary studies on the efficacy of sodium salt solutions in the treatment of shock.

Rosenthal (1942–5) has stated that the administration of sodium salt solutions has reduced the mortality in mice suffering from shock caused by thermal burns, trauma, and haemorrhage, the oral or intraperitoneal route being more effective than the intravenous route. Fox (quoted by Rosenthal, 1943) has followed up this work clinically, giving isotonic sodium lactate in large quantities (5–11 litres in 24 hours) by mouth to patients suffering from thermal shock, and all his patients got well. Allen (1943) and Prinzmetal *et al.* (1943) have also reported good results when using physiological salt solutions for the treatment of shock due to thermal burns in dogs and mice respectively. In view of this success in the treatment of shock by large volumes (5–10% of the body weight) of normal saline, it was decided to test the efficacy of such a therapy in lewisite shock.

In the present tests four species of animal were used—viz., mice, rats, guinea-pigs, and rabbits. Subcutaneous injection of lewisite oxide (L.O.) was found to produce uniform and repeatable mortalities in all species. Two methods of assessment were employed. (1) Massive dosages of L.O. given, to produce 100% mortalities rapidly (6–12 hours). Therapies which significantly prolonged the median survival time were tested by method 2. (2) Dosages to produce a high proportion of deaths were given and the percentage mortalities of the treated and untreated groups were compared.

Mice

Mice weighing 20 g. were used throughout. The L.O. was injected subcutaneously in 0.2 ml. of water. As Rosenthal's mortalities are given only for acute mortalities (i.e., the first 48 hours) from shock, our stated mortalities are also acute mortalities. By this means it was hoped that deaths from secondary complicating factors would not complicate the picture.

EXPERIMENT A.—*Results of Dosage of Lewisite Oxide 9 mg./kg. at Z hours*

Quantity of 0·9% Saline given Intraperitoneally (ml.)	When given (minutes)	Median Survival Time in Hours (5 Mice per Group)	Conclusions
Nil		5·9 (25 mice)	(1) 2 ml. saline given. In 30 minutes L.O. produced a significant increase in median survival time (P = 0·03) (2) So did 4 ml. given 2 hours after L.O. (P = 0·05) (3) In general, 4-ml. doses of saline were better the later they were given; 2-ml. doses were better the earlier they were given (4) In general, saline given before L.O. was good (P = 0·05), and 2 ml. saline given before L.O. was good (P = 0·05) (5) All dosages of saline, whether given before or after the L.O., increased the survival time. Saline given at the same time as the L.O. did not
0·5	Z − 30	8·1	
0·5	Z	5·7	
0·5	Z + 30	9·3	
0·5	Z + 60	9·3	
0·5	Z + 120	6·2	
1·0	Z − 30	6·8	
1·0	Z	4·5	
1·0	Z + 30	8·3	
1·0	Z + 60	6·6	
1·0	Z + 120	8·2	
2·0	Z − 30	10·5	
2·0	Z	7·1	
2·0	Z + 30	17·4	
2·0	Z + 60	6·9	
2·0	Z + 120	7·2	
4·0	Z − 30	8·9	
4·0	Z	4·8	
4·0	Z + 30	8·3	
4·0	Z + 60	8·3	
4·0	Z + 120	13·5	

EXPERIMENT B.—*Dosage of Lewisite Oxide 9 mg./kg. at Z hours*

Total Quantity 0·9% Saline Injected Intraperitoneally (ml.)	How Injected	Median Survival Time in Hours (5 Mice per Group)	Conclusions
2·0	2 ml. at Z + 30 min.	6·4	The following methods of administration of saline significantly increased the median survival time: (1) 1 ml. at 1/2 and 1 hr.: P = 0·001 (2) 4 ml. in 3 doses: P = 0·01 (3) 4 ml. in 4 doses: P = 0·05 (4) 6 ml. in 3 doses: P = 0·05 (5) 2 ml. in 5 doses: P = 0·05 The 4-ml. and 6-ml. therapies are better when given in divided doses over a long period
2·0	1 ml. at Z + 30 and Z + 60 min.	20·0	
2·0	0·7 ml. at Z + 30, 60, and 90 min.	12·3	
2·0	0·5 ml. at Z + 30, 60, 90, and 120 min.	13·2	
4·0	4 ml. at Z + 30 min.	11·2	
4·0	2 ml. at Z + 30, Z + 60	12·0	
4·0	1·3 ml. at Z + 30, 60, and 90 min.	15·8	
4·0	1 ml. at Z + 30, 60, 90, and 120 min.	14·1	
6·0	6 ml. at Z + 30	12·9	
6·0	6 ml. at Z + 30, Z + 60	12·6	
6·0	2 ml. at Z + 30, 60, and 90 min.	13·2	
6·0	1·5 ml. at Z + 30, 60, 90, and 120 min.	10·0	
Nil	—	6·7 (8 mice)	

EXPERIMENT C.—*Dosage of Lewisite Oxide 10 mg./kg. at Z hour. 2 ml. of Salt Solution given Intraperitoneally at Z+30 minutes*

Strength of Solution	Solute	Median Survival Time in Hours (5 Mice per Group)	Conclusions
Nil	Nil	3·61 (8 mice)	(1) In general, the chloride ion is more effective than the sulphate ion (2) In general, the sodium ion is more effective than the potassium ion (P = 0·001). The equimolecular mixture of sodium and potassium ions was intermediate in effectiveness (P = 0·05, cf. potassium solutions) (3) The weaker solutions (N and N/4) are more effective than the stronger (4N) (P = 0·001)
4N	NaCl	2·04	
N	,,	4·79	
N/4	,,	5·01	
4N	KCl	0·741	
N	,,	0·87	
N/4	,,	5·75	
4N	Equimolecular mixture of NaCl and KCl	1·05	
N	,,	2·69	
N/4	,,	2·40	
4N	Sodium sulphate	1·38	
N	,,	1·29	
N/4	,,	3·55	
4N	Potassium sulphate	0·63	
N	,,	0·79	
N/4	,,	1·55	
4N	Equimolecular mixture of NaSO and KSO	0·63	
N	,,	1·05	
N/4	,,	4·47	

EXPERIMENT D.—*Dosage of Lewisite Oxide 10 mg./kg. at Z hours*

At Z−30 minutes 2 ml. of the following fluids were given intraperitoneally (30 mice per group):

Normal saline	Median survival time, 5·7 hours
Distilled water	,, ,, ,, 5·0 ,,
Untreated	,, ,, ,, 4·1 ,,

Hence: (1) The normal saline caused a significant increase in the median survival time (P=0.02). (2) The water did not cause a significant increase in the median survival time (P=0.07).

EXPERIMENT E.—*Dosage of Lewisite Oxide 9 mg./kg. at Z hours. Results from the Intraperitoneal Injection of 0.9% Saline*

Total Dose of Saline	Temp. of Saline	How Injected	Median Survival Time in Hours (5 Mice per Group)
2 ml.	39° C.	2 ml. at Z + 30 min.	8·3
	17° C.	,,	8·1
	39° C.	1 ml. at Z + 30 and Z + 60 min.	7·9
	17° C.	,, ,,	5·2
	39° C.	4 ml. at Z + 30 min.	5·5
	17° C.	,,	5·0
4 ml.	39° C.	1·3 ml. at Z + 30, Z + 60, Z + 90 min.	9·1
	17° C.	,, ,, — ,, ,,	4·8
Nil	—		5·2 (25 mice)

Here (1) if a single dose is given, 2 ml. is effective but not 4 ml., and it is of little importance whether the saline is warm or not; (2) if divided doses are given, 2 ml. and 4 ml. are equally satisfactory, but only the warm saline is effective.

From these preliminary experiments it was concluded that, in mice, for the treatment of shock caused by the subcutaneous injection

of L.O., warm (39° C.) normal saline given either as one 2-ml. dose 30 minutes after the L.O. or in two 1-ml. doses 30 and 60 minutes after the L.O. was the best of the therapies tested. Its effectiveness in reducing the percentage mortality from the acute shock of lewisite poisoning was next tested. The quantities used were: 2 ml., given 30 minutes after L.O.; 1 ml., given 30 and 60 minutes after L.O.; 1 ml., given 60 minutes after L.O. (Rosenthal's technique). 1 ml. sodium lactate, given 30 and 60 minutes after L.O., was also assessed, as Rosenthal had reported sodium lactate to be as effective as sodium chloride.

The results obtained are summarized in the following table:

Experiment	Dosage of L.O. (mg./kg.)	Therapy: Amount of 0·9% Saline	Therapy: Time of Admin. after L.O.	No. of Mice Used	Deaths in 48 Hours: No.	Deaths in 48 Hours: %
F	4	1 ml.	60 min.	50	11	22
	4		Nil	50	21	42
G	4·5	1 ml.	30 and 60 min.	50	22	44
	4·5		Nil	50	42	84
H	4·5	2 ml.	30 min.	50	19	38
	4·5		Nil	50	33	66
	4·5	1 ml.	30 and 60 min.	20	8	40
I	4·5	1 ml. N sodium lactate	30 and 60 min.	20	5	25
	4·5		Nil	20	19	95

Hence all these therapies produced a significant reduction of the mortality, the sodium lactate being as good as sodium chloride.

Rats

Rats weighing 150 g. were used and the lewisite was produced by the subcutaneous injection of 4.5 mg./kg. of L.O. In mice it has been found that 10% of the body weight (i.e., 2 ml.) of saline was effective when given 30 minutes after intoxication. In rats, therefore, we gave 10% of the body weight (i.e., 15 ml.) of 0.9% saline intraperitoneally 60 minutes after the injection of the L.O. The following 21-day mortalities were obtained:

Untreated group of 50 rats: deaths in 21 days 47 (94%)
Treated group of 50 rats: deaths in 21 days 9 (18%)

Guinea-pigs

A preliminary experiment was carried out to determine the optimum conditions for the administration of the 0.9% saline. 500-g. pigs were used, and to each of them 8 mg./kg. L.O. was given subcutaneously at Z hours. Results:

Total Quantity of 0·9% Saline Injected	How Injected	Median Survival Time in Hours (10 Pigs per Group)
12 ml.	12 ml. at Z + 40 min.	4·6
	12 ml. at Z + 80 min.	4·4
	6 ml. at Z + 40 and Z + 80 min.	2·6
25 ml.	25 ml. at Z + 40 min.	7·5
	25 ml. at Z + 80 min.	3·1
	12 ml. at Z + 40 and Z + 80 min.	1·9
50 ml.	50 ml. at Z + 40 min.	5·0
	50 ml. at Z + 80 min.	4·2
	25 ml. at Z + 40 and Z + 80 min.	2·9
Nil	—	4·5

From this experiment it was concluded that 25 ml. of 0.9% saline given intraperitoneally 40 minutes after the injection of the L.O. was the best method of administration tried.

A second experiment was then performed, giving 4 mg./kg. L.O. to 500-g. guinea-pigs followed by 25 ml. of 0.9% saline intraperitoneally 40 minutes later. A significant (P=0.02) reduction in mortality was produced, as follows:

60 guinea-pigs untreated: deaths in 21 days 31 (52%)
60 „ treated with saline: deaths in 21 days .. 20 (33%)

Rabbits

When given intraperitoneally, large quantities of normal saline would appear to be ineffective in rabbits intoxicated with L.O. and, indeed, in themselves to be harmful:

Number of Rabbits (2 kg.)	Dose of L.O. at Z hr. (mg./kg.)	Treatment	Deaths in 48 Hours
5	6	6 × 50 ml. N saline at Z + 4, 8, 12, 24, 28, and 32 hours	4
5	6	Nil	4
5	Nil	6 × 50 ml. N saline at Z + 4, 8, 12, 24, 28, and 32 hours	2

The effect of a normal solution of sodium lactate was next examined. Preliminary trials suggested that 2-kg. rabbits were least distressed when two 75-ml. doses were given by mouth with an interval of two hours between doses. Rabbits were therefore injected subcutaneously with L.O. (4 mg./kg.), and to half of them, two hours later, 75 ml. of normal sodium lactate was given by mouth, followed by a similar quantity in a further two hours. The resulting mortalities were:

25 2-kg. rabbits, untreated: deaths in 21 days 22 (88%)
25 „ „ treated „ „ 14 (56%)

This reduction in mortality is significant at P=0.01.

Discussion

Rosenthal, using mice, Fox, in humans, Allen, using dogs, and Prinzmetal *et al.*, also using mice, have already reported favourably on the efficacy of sodium salt solutions in the early treatment of shock due to various causes. Large quantities (5 to 10% of the body weight) must be given, and Allen has suggested that shock is a condition of tissue thirst, which can be adequately satisfied only by giving large quantities of physiological saline. Indeed, he intimates that the reason that physiological saline has failed in the past in the treatment of shock is that a sufficient volume has not been given; the presence of haemoconcentration after the administration of saline is not an indication of the uselessness of saline therapy, but merely means that the amount given was insufficient.

Our experiments have shown that large quantities of sodium salt solution do reduce the mortality from shock due to lewisite oxide, but that different species do not respond with equal facility. The order of efficacy of sodium salt solutions in the treatment of shock in the four species tested descends as follows: rats, mice, guinea-pigs, and rabbits. This is also, in our experience, the descending order of the ability of the different species to tolerate large quantities of sodium salt solution.

Rosenthal's work intimates that there is a loss of fluid and sodium to the shocked tissues; our results support this view. We have not had the opportunity of confirming the suggestion that the shocked animal is hypersensitive to potassium, but we agree that the beneficial effect of the sodium administration can be offset by the simultaneous administration of potassium.

Summary

The efficacy of sodium salt solutions in the treatment of shock produced by the subcutaneous injection of lewisite oxide has been assessed in four species of animals—mice, rats, guinea-pigs, and rabbits. It is concluded that large quantities of sodium chloride or sodium lactate solution do reduce the mortality from lewisite shock, but that different species do not respond with equal facility.

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PENICILLIN: INCREASED STANDARD OF PURITY

The Ministry of Health makes the following announcement: Preparations of penicillin were added to the Schedule to the Therapeutic Substances Act by provisional Regulations in August, 1944. As a result of fuller experience of these preparations it has become necessary to replace the provisional Regulations by new ones. This has now been done by the Minister of Health, the Secretary of State for Scotland, and the Minister of Health and Local Government, Northern Ireland. The new Regulations provide for: (1) An increased standard of purity for preparations to be used for parenteral injection, by exclusion of the crude filtrates permitted under the provisional Regulations, and the requirement that penicillin shall be issued only in the form of a dry salt or other dry substance, or in some form approved by the licensing authority. (2) An increase in the minimum potency to 300 units per milligramme for preparations in solid form, and to 2,000 units per cubic centimetre [ml.] for preparations in solution.