

## STUDIES IN THE METABOLISM OF SODIUM *r*-LACTATE. II. RESPONSE OF HUMAN SUBJECTS WITH ACIDOSIS TO THE INTRAVENOUS INJECTION OF SODIUM *r*-LACTATE

BY ALEXIS F. HARTMANN AND MILTON J. E. SENN

(From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital, St. Louis)

(Received for publication September 10, 1931)

In the first paper of this series it has been demonstrated that sodium *r*-lactate is completely metabolized within a period of from one to two hours by normal individuals when given in a dose of 7 cc. of molar solution per kilogram over a period of one-half hour. The utilization of the racemic mixture of lactate probably involves the oxidation of a fraction of the lactate radicle and the conversion into glycogen of the remainder, as well as the liberation of the sodium ion, which then is excessive in the body fluids and is excreted into the urine.

In the present study the effect of intravenous sodium lactate upon the carbon dioxide content of the blood in patients with acidosis was investigated. For the sake of convenience, the cases have been divided into three groups: (1) those with acidosis secondary to renal insufficiency, (2) those with acidosis associated with diarrhea, dehydration and oliguria, and (3) those associated with diabetes mellitus.

### *Nephritic acidosis*

The acidosis associated with renal insufficiency is brought about rather simply, being due almost entirely to the accumulation of such acids as phosphoric and sulphuric, and to the loss of fixed base from the body fluids, because of the impairment of renal function (1). Except in the terminal stages the circulation of the blood is practically normal, as is also apparently the ability on the part of the subject to oxidize and store carbohydrate. This type of acidosis, therefore, from theoretical considerations, should be promptly relieved by the administration of sodium lactate in sufficient amounts. In Table 1 are recorded the results to date of treatment of this type of acidosis with sodium *r*-lactate. It should be noted that, except in one instance, the expected increase in the carbon dioxide content was fairly close to that actually observed, and in the averages of four instances cited there was a discrepancy of only 1.6 per cent. In the one instance in which this discrepancy was considerably greater (— 13.4 volumes per cent) the explanation may be that only one

TABLE 1  
*Effect of intravenous administration of sodium  $\tau$ -lactate on plasma CO<sub>2</sub> content*  
*Cases of acidosis associated with chronic nephritis*

History number	Age <i>years</i>	Date	Body weight <i>kgm.</i>	Body water <i>liters</i>	Molar sodium lactate <i>cc.</i>	Plasma CO <sub>2</sub> content			Difference <i>volumes per cent</i>	Remarks
						Before <i>volumes per cent</i>	After ( ) hours <i>volumes per cent</i>	Expected <i>volumes per cent</i>		
G-198	7	October 24, 1930	17.0	11.4	112	20.8	51.3 (4)	42.8	+ 8.5	Chronic suppurative nephritis associated with urethral obstruction and cystitis.
		October 30, 1930	17.2	11.5	110	33.1*	41.1*(1)	54.5	- 13.4	
		February 6, 1931	18.1	12.1	100	30.1*	48.4*(2)	48.9	- 0.5	
0	33	December 1, 1930	60. $\pm$	40.2	240	36.8	49.3(2)	50.2	- 0.9	Chronic glomerular nephritis
								Average =	- 1.6	

\* Determinations on whole blood.

hour elapsed after the beginning of the injection and the taking of the next blood sample.

*Acidosis associated with diarrhea, dehydration and oliguria*

This type of acidosis results from more complex factors than does the nephritic type. As in the latter, there is always loss of fixed base from the body fluids. There is also a loss of acid radicles, and in some instances water loss is so great that despite the loss of minerals from the body fluids the actual chloride and total base concentrations observed may be greater than normal. Associated with the diminished volume and flow of the blood, there is a diminished urinary secretion, and while it lasts the same factors that contribute towards the formation of acidosis seen in chronic renal insufficiency are at work. Occasionally, particularly in the restless infant or the infant with convulsions, lactic acid accumulates in the body fluids. Such an accumulation is looked upon as due essentially to anoxemia, which seems due largely to the reduced blood flow. Aside from these considerations another factor should be mentioned, at least. At autopsy evidence of liver damage is frequently noted in this type of patient. It is quite possible that such liver damage might interfere with the normal metabolism of lactic acid diffusing from the muscles into the blood stream.

In Table 2 are included all the results to date of the treatment of this type of acidosis with carefully measured amounts of the racemic lactate preparation.<sup>1</sup> It should be noted that in all six instances, although an increase in the carbon dioxide content occurred, which brought the patient well out of the danger zone of acidosis, nevertheless, the observed rise fell short of that predicted. The discrepancy varied from 5.5 to 24.9 volumes per cent, the average being 12.1 volumes per cent.

There are probably a number of factors contributing to this discrepancy. Because of the dehydration of the body the administration of a watery solution of sodium lactate will tend to dilute the body fluids, and by dilution to reduce the concentration of the salts (including sodium bicarbonate) present. Then, as has been shown previously (2) acidosis of this type is frequently uncompensated and low pH values may occur. With the partial restoration of sodium bicarbonate to the body fluids there would be of course a restoration of pH which would tend to cause a withdrawal of a certain amount of base bound to bicarbonate for combination with other ions, such as protein. In addition to these factors, the

---

<sup>1</sup> The use of the mixture of sodium *r*-lactate and hypotonic Ringer's solution made by Eli Lilly and Company and designated as Physiological Buffer Salts Solution has been routine in the wards of the St. Louis Children's Hospital for more than two years. Use of this very much larger amount of material in this paper is impossible because of the minimal amount of blood chemistry study which seemed required in the successful treatment of these patients.

TABLE 2

*Effect of intravenous administration of sodium r-lactate on plasma CO<sub>2</sub> content  
Cases of acidosis associated with diarrhea—dehydration—oliguria*

History number	Age	Date	Body weight	Body water	Molar sodium lactate	Plasma CO <sub>2</sub> content			Difference
						Be-fore	After ( ) hours	Ex-pected	
	months		kgm.	liters	cc.	vol-umes per cent	volumes per cent	volumes per cent	volumes per cent
G-2058	16	October 28, 1930	7.2	4.8	90	27.5	44.6(2)	69.5	— 24.9
G-2352	1	November 23, 1930	2.7	1.8	20	26.9	46.3(4)	51.8	— 5.5
G-2127	3	December 14, 1930	4.7	3.2	45	23.5	42.5(3)	55.0	— 12.5
G-814	32	August 5, 1930	9.5	6.4	80	29.5	49.8(2)	56.5	— 6.7
H-479	9	February 28, 1931	7.0	4.7	60	23.6	46.5(3)	52.4	— 5.9
H-669	1	March 14, 1931	2.7	1.8	30	23.9	43.8(3)	61.2	— 17.4
						Average =			— 12.1

original cause of the acidosis, the diarrhea entailing the loss of gastrointestinal secretions, continues to be effective, so that while acidosis is being relieved by administration of alkali, some of this restored alkali is being excreted out into the lumen of the bowel.

An interesting point, which has come to light in the treatment of this type of acidosis, concerns the behavior of the lactic acid concentration of the blood of such cases. Even though lactic acid may be abnormally high before the injection of sodium *r*-lactate, normal values are usually seen two or three hours after the injection. The explanation, in all probability, lies in the effect of the increased blood flow on utilization of lactic acid. Occasionally, however, in the presence of marked disturbance of circulation which persists after the administration of fluids, the metabolism of lactate seems delayed. In such cases the administration of oxygen by means of the oxygen tent seems of value in hastening oxidation.

Another point of extreme interest is the fact that the metabolism of sodium lactate may be accomplished right up to the point of death. Thus, Case G-2058 was dying from a hemolytic streptococcus septicemia, mastoiditis and pyuria when the test was begun (for the therapeutic purpose of relieving the acidosis). Although the patient died about four hours after the administration of the sodium lactate, the plasma carbon dioxide content had increased from 27.5 to 44.6 volumes per cent during the first half of this period. Similar phenomena were encountered in Case G-2127, death here also being due to infection and occurring within twelve hours after relief of acidosis, following the lactate administration.

*Diabetic acidosis*

Severe diabetic acidosis is also due to complex causes (3). One factor of importance is, of course, the accumulation of the organic acids which tend to displace the bicarbonate ion from combination with base. Other significant factors are, however, the loss of fixed base from the body fluids, which occurs during the period of polyuria and of vomiting, and the later effect of anhydremia on renal function, which is similar to the effect of anhydremia in the dehydrated infant with diarrhea; that is, essentially there is renal insufficiency which permits phosphoric and sulphuric acid to accumulate and which prevents excretion of these anions and others, such as chloride and the ketone acids, free of base or bound to ammonia. In addition to these factors there is, of course, the altered carbohydrate metabolism, secondary to insulin insufficiency.

In Table 3 are recorded the results to date of the treatment of this type of acidosis with sodium *r*-lactate. If we consider first the results obtained when no insulin was administered simultaneously, we note that in Case G-1214 who was not in a very critical condition, the rise of the carbon dioxide content of the blood after three hours was somewhat in excess (8.8 volumes per cent) of that predicted. In all probability, therefore, in addition to complete release of base bound to the lactate ion, base was also released from other anions. In Case G-2520, however, the observed carbon dioxide content was 16.6 volumes per cent less than expected. In this instance the acidosis was more severe and the factors inducing the production of acidosis were apparently operating more intensively. In this instance, also, there was clinically more dehydration and less diuresis.

TABLE 3

*Effect of intravenous administration of sodium r-lactate on plasma CO<sub>2</sub> content  
Cases of acidosis associated with diabetes mellitus*

Case number	Age	Body weight	Body water	Molar sodium lactate	Plasma CO <sub>2</sub> content			Difference	Remarks
					Be-fore	After ( ) hours	Ex-pected		
	years	kgm.	liters	cc.	volumes per cent	volumes per cent	volumes per cent	volumes per cent	
G-1214	7	25.±	16.8	120	34.8	59.6(3)	50.8	+ 8.8	No insulin given
G-2520	12	35.0	23.5	235	25.4*	31.2*(2)	47.8	- 16.6	No insulin given
G-1313	2	10.0	6.7	80	29.7	56.9(3)	56.4	+ 0.5	15 units insulin given
H-1054	12	33.7	22.4	210	15.0	42.0(2)	36.0	+ 6.0	40 units insulin given
G-463	11	45.±	30.1	630	8.5	34.8(2)	56.0	- 21.2	100 units insulin given
					Average = - 4.5				

\* Determinations on whole blood.

If we turn next to the two instances in which insulin was given along with sodium *r*-lactate, we find that in one case (G-1313), moderately severe acidosis was completely relieved and the observed rise in the carbon dioxide content was almost identical with that predicted. In another (H-1054), the carbon dioxide content rose from 15 to 42 volumes per cent in two hours, the increase being 6 volumes per cent more than expected. In case G-483, however, we find that a marked discrepancy occurred and a much lower carbon dioxide content was observed than predicted, even though two hours had elapsed after the injection of lactate. In addition to the very marked dehydration and acidosis a number of factors seemed responsible for this discrepancy. An unusually large dose of lactate was given (14 cc. molar per kilogram of body weight). Two hours after the injection the blood lactic acid was still 100 mgm. per 100 cc. At this time the body temperature had risen to 42.8° C., and the pulse was so rapid that it could not be accurately counted. Two hours later, without regaining consciousness, the patient died. At the time of death, approximately four hours after the administration of the lactate, the blood lactic acid was still elevated, 55 mgm. per 100 cc. The carbon dioxide content at this time was 36.8 volumes per cent. In all probability the hyperpyrexia was the result of the specific dynamic action of lactate in stimulating metabolism, and to us it seemed that it was an important factor in causing death, although the patient was desperately ill before treatment was started. Until further studies have been made upon the effect of heat production from lactate administration, we feel that a dose of 7 cc. of molar solution per kilogram of body weight should not be exceeded, particularly in the diabetic subject who also receives insulin.

In Table 4 are included data which indicate the effect of the intravenous administration of *sodium bicarbonate* on the plasma carbon dioxide content of patients with different types of acidosis. In general, the same type of agreement and discrepancy between the predicted and the observed carbon dioxide contents were noted.

From the data discussed above it seems that one can predict fairly well the effect of any given dose of sodium *r*-lactate on an individual with acidosis, providing the dose is not so large as to let too marked alkalosis develop, which would complicate matters. In applying this data so that it might be of assistance clinically, we have calculated in the following manner the dose of molecular sodium lactate or bicarbonate necessary in individual cases to restore any observed carbon dioxide content of the body fluids to normal within a period of two to three hours:

1. Body water (blood, lymph, spinal fluid, muscle water, etc.) equals 80 to 70 per cent (approximately two-thirds) of body weight.
2.  $\text{BHCO}_3$  of entire body water approximates  $\text{BHCO}_3$  of plasma.
3. One cc. molecular  $\text{NaHCO}_3$  per liter of body water equals 2.24 cc. of  $\text{CO}_2$  per 100 cc. (2.24 volumes per cent  $\text{CO}_2$ ).

TABLE 4  
*Effect of intravenous administration of  $\text{NaHCO}_3$  on plasma  $\text{CO}_2$  content*

Case	Body weight kgm.	Molar $\text{NaHCO}_3$ cc.	Plasma $\text{CO}_2$ content			Differ- ence	Plasma pH		Remarks
			Before	After ( ) hours	Expected		Before	After ( ) hours	
A.W.	8.26	95	volumes per cent 55.7	volumes per cent 96.5(1)	volumes per cent 94.2	+ 2.3	7.47	7.58(1)	Acute "pyelitis"; no renal insufficiency
K.P.	6.1	60	15.5	64.5(8)	48.3	+ 16.2	7.12		Marked ketosis; glucose also administered
R.D.	16.2	119	24.0	54.6(16)	48.5	+ 6.1	7.33	7.45(16)	Marked renal insufficiency; Ringer's solution also administered
W.S.	4.0	75	12.9	43.2(2)	74.4	- 31.2			Diarrhea, dehydration and oliguria
V.N.	27.3	119	15.5	23.7(3)	29.5	- 5.8			Diabetic coma; insulin also administered
A.S.	30.0	95	10.6	16.1(3)	23.2	- 7.1			Diabetic coma; insulin also administered
N.G.	27.0	150	15.0	40.3(3)	33.7	+ 6.6	7.10		Diabetic coma; insulin, glucose and Ringer's solution also administered
E.S.	23.6	300	18.7	22.8(3)	37.7	- 14.9		7.15(3)	Diabetic coma; insulin, glucose and Ringer's solution also administered
	23.6	150	7.4	92.5(8)	28.7	+ 54.8	7.00	7.57(8)	
				53.8(8)		+ 25.1	7.05	7.43(8)	

4. Therefore, expected increase in volumes per cent  $\text{CO}_2$  equals 
$$\frac{2.24 \times \text{cc. molecular NaHCO}_3 \text{ or Na lactate}}{\text{liters body water}}$$
5. Or, dose of molecular  $\text{NaHCO}_3$  or Na lactate to increase  $\text{CO}_2$  content of body water to 60 volumes per cent equals 
$$\frac{60 - \text{CO}_2 \text{ content}}{2.24}$$
  
 $\times$  liters body water. A more workable expression of this equation is, dose of molecular Na lactate equals  $(60 - \text{CO}_2 \text{ content}) \times (0.3 \times \text{body weight in kgm.})$ .

We feel that this method of calculating the dose of molar sodium  $\gamma$ -lactate is perfectly safe as regards the treatment of nephritic acidosis, as observed values will agree closely to those predicted. In the case of acidosis associated with diarrhea, dehydration and oliguria, the observed increase will be less than the predicted, but in all probability, sufficient to bring the patient well out of the danger zone. In the case of diabetic acidosis the other measures of value in the treatment of acidosis, such as administration of insulin, carbohydrate and Ringer's solution, should, of course, be carried out. In this type of acidosis, because of the synergistic effect of insulin, the dose of sodium lactate calculated to raise the carbon dioxide content 15 to 20 volumes per cent should be sufficient and should not result in a dangerous increase in heat production.

#### SUMMARY AND CONCLUSIONS

The response of subjects with acidosis to the intravenous injection of sodium  $\gamma$ -lactate was studied, with the following results:

1. Sodium  $\gamma$ -lactate is metabolized in practically a normal fashion in subjects with acidosis.
2. In the three chief types of acidosis (nephritic, diarrheal and diabetic) the increase in the carbon dioxide content of the blood can be fairly accurately predicted.

#### BIBLIOGRAPHY

1. Hartmann, A. F., and Darrow, D. C., J. Clin. Invest., 1928, vi, 127. Chemical Changes Occurring in the Body as a Result of Certain Diseases in Infants and Children. II. Acute Hemorrhagic Nephritis. Sub-Acute Nephritis; Severe Chronic Nephritis.
2. Hartmann, A. F., Am. J. Dis. Child., 1928, xxxv, 557. Chemical Changes Occurring in the Body as the Result of Certain Diseases. I. The Effects of Diarrhea, Vomiting, Dehydration and Oliguria on the Acid-Base Balance of the Plasma of Infants with Mastoiditis.
3. Hartmann, A. F., and Darrow, D. C., J. Clin. Invest., 1928, vi, 257. Chemical Changes Occurring in the Body as the Result of Certain Diseases. III. The Composition of the Plasma in Severe Diabetic Acidosis and the Changes Taking Place During Recovery.