STUDIES IN THE METABOLISM OF SODIUM *r*-LACTATE. I. RESPONSE OF NORMAL HUMAN SUBJECTS 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 recently published studies, Hartmann and Darrow (1, 2, 3) emphasized the fact that if sodium bicarbonate were properly administered along with other indicated therapeutic measures, severe acidosis could be much more effectively treated. There were recognized, however, a number of objections to the administration of sodium bicarbonate. The most serious was that, if given intravenously in amounts large enough to insure effectiveness, it tended to produce too rapid a change in the reaction of the body fluids, and often resulted in an almost immediate shift from uncompensated acidosis to uncompensated alkalosis, even though the sodium bicarbonate content of the body fluids was not made abnormally high; i.e., the ratio $\frac{BHCO_3}{H_2CO_3}$ increased because the numerator was added to more rapidly than the denominator could be increased by the production of carbon dioxide in the tissues and its accumulation in the body fluids through reduced pulmonary ventilation. This danger was usually avoided by giving the alkali in fractional dosages and checking the effect by chemical examination of the blood. The latter constituted another objection, particularly in the case of the young infant. Other disadvantages lay in the fact that if sodium bicarbonate were to be injected subcutaneously or intraperitoneally, it had first to be sterilized by Berkefeld filtration, and then rendered less irritatingly alkaline by bubbling carbon dioxide through it.[1] Unless sealed, such a mixture would of course become too alkaline again as a result of loss of carbon dioxide. Another disadvantage lay also in the fact that the injection of sodium bicarbonate alone tended, at least theoretically, to disturb the ionic balance between sodium, potassium, calcium and magnesium.

In order to overcome those objections the mixture of sodium lactate and hypotonic Ringer's solution was devised (5). The conversion of

[1] Cunningham and Darrow (4) have recently overcome this objection by partly neutralizing sodium bicarbonate previously sterilized in the dry state with hydrochloric acid.

sodium lactate into sodium bicarbonate, it was felt, would be sufficiently slow to permit maintenance of the proper $\frac{BHCO_3}{H_2CO_3}$ ratio, which would lessen the danger of alkalosis and possibly even permit quantitative restoration of diminished body fluid sodium bicarbonate by a single dose. Sodium lactate, alone or combined with Ringer's solution, is non-irritating, stable and can be sterilized readily by boiling.

The clinical results with this mixture of salts have been more than gratifying, particularly in connection with its use in the treatment of infants with acidosis resulting from diarrhea, dehydration and oliguria. Nevertheless, we have felt it wise to study more thoroughly the response to sodium lactate under various abnormal conditions, and to try to determine the limits of its effectiveness and safety. It seemed quite possible, for instance, that the complete metabolism of sodium lactate with conversion into sodium bicarbonate might be seriously impaired when liver damage or anhydremia and anoxemia were present. It also seemed more than likely that, when given in excess to subjects with diminished body fluid electrolytes or renal insufficiency, sodium bicarbonate might remain in excess in the body fluids, leading to dangerous alkalosis.

To determine the fate of intravenously injected sodium r-lactate in normal or essentially normal individuals, children who either had completely recovered from an acute illness or who were suffering from some minor disease were selected from the wards of the St. Louis Children's Hospital. In all instances these subjects were apparently normal in respect to the circulation of the blood and hepatic and renal functions. The procedure was as follows:

In the fasting state in the morning, a control sample of venous blood was secured for determination of carbon dioxide content, glucose, lactic acid and inorganic phosphate. The chemical methods were the same as those used previously (6). Faintly alkaline sodium r-lactate [2] was then injected intravenously, in a dose of approximately 4 to 7 cc. of molar solution per kilogram of body weight. To avoid the effects of a too hypertonic solution, the molar preparation was usually diluted with 1 to 2 volumes of distilled water or hypotonic Ringer's solution before the injection. The latter usually required about 30 minutes. Blood samples were again secured for chemical determinations, usually 15, 30, 60, 120 and

[2] Molar sodium r-lactate was made by neutralizing concentrated (approximately 10 molar) lactic acid with approximately 50 per cent sodium hydroxide, with phenol red as the indicator. Because of the anhydride present in the concentrated preparation, the latter was first diluted to about 8 volumes with distilled water and kept boiling slowly, alkali being added to slight excess until all the anhydride was hydrolyzed and neutralized, which usually required from 30 to 45 minutes. A final dilution of 1 : 10 was then made.

240 minutes after the end of the injection. During this period urine specimens were collected and kept under oil until their carbon dioxide contents could be determined.

RESULTS

Blood lactate. Although no check was made by determining the blood lactic acid immediately after injection, the quantity of sodium *r*-lactate was such as to raise the blood lactic acid approximately 300 to 500 mgm. per 100 cc. The rapid fall which occurs during the first 15 minutes after injection is sufficient to reduce such a concentration to approximately 30 to 65 mgm. per 100 cc. (Table 1 and Chart 1). In other

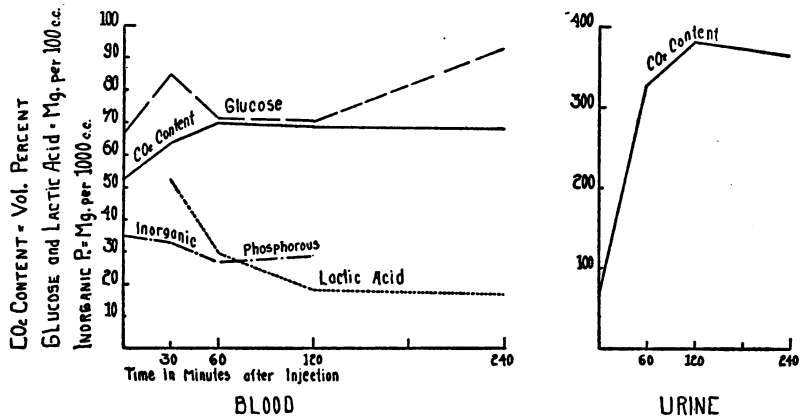

CHART 1. THE AVERAGE RESPONSE OF NORMAL SUBJECTS TO THE INTRAVENOUS ADMINISTRATION OF 6.75 CC. OF MOLAR SODIUM *r*-LACTATE PER KILOGRAM OF BODY WEIGHT

(Average of Cases G-336, G-1982, F-2131 and H-925)

words, about 90 per cent of the injected lactate has left the blood stream during the first quarter of an hour. The disappearance of lactate from the blood then continues at a somewhat slower rate. After one-half hour its concentration is usually slightly greater than before the injection, while after one hour it is practically normal. At the end of two hours a subnormal level is often reached.

The initial rapid fall is probably the result of several factors: (1) diffusion into the body fluids, (2) oxidation and conversion into glycogen, and (3) excretion into the urine. The latter is probably the least important as but relatively little lactic acid appears in the urine. Quantitative study of this phase is in progress.[3] The later more gradual fall seems due

[3] The amount excreted seems to vary with the rate of injection and the urinary volume. The greatest amount excreted, which we have observed to date, is about 18 per cent.

TABLE 1

Response of normal human subjects to the intravenous injection of sodium r-lactate

Case number	Age	Weight	Molar sodium *r*-lactate		Blood							Urine	
			Dose and diluent *	Per kgm. of body weight	Minutes after injection	Type of blood sample †	CO_2 content	Lactic acid	Glucose		Inorganic phosphorus	Minutes after injection ‡	CO_2 content
									True	Apparent			
	years	*kgm.*	*cc.*	*cc.*			*volumes per cent*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		*volumes per cent*
G-2078	5	18.5	130	7.0	0	WB	52.1	17.8	70.0	73.0			
					15	WB	63.5	63.0	73.0	87.0			
					30	WB	66.6	53.6	95.0	106.0			
					60	WB	65.3	18.9	64.0	73.0			
					120	WB	64.5	12.6	64.0	73.0			
G-2155	12	33.9	140	4.1	0	WB	54.7	16.4	56.0	67.0		0	40.0
					15	WB	59.1	38.4	86.0	99.0			
					30	WB	60.9	32.7	86.0	99.0		30	127.0
					60	WB	64.5	21.4	83.0	113.0		60	273.0
					120	WB	59.1	16.4	58.0	87.0		120	35.3
G-2114	9	27.3	110	4.0	0	WB	53.7	24.5	107.0	112.0			
					15	WB	57.6	41.6	122.0	125.0			
					30	WB	57.0	23.0	110.0	112.0			
					60	WB	58.6	16.4	70.0	73.0			
					120	WB	57.1	11.5	62.0	64.0			
G-336	14	42.6	245	5.8	0	P	56.4				4.0		
			+		0	WB	51.1	27.7	56.4	70.0		0	3.1
			200 R		30	P	64.0				3.8		
					30	WB	56.4	63.6	76.0	99.0			
					60	P	75.9				2.8		
					60	WB	66.6	30.3	76.0	86.0		60	350.0
					120	P	70.0				3.3		
					120	WB	64.9	20.1	65.0	80.0		120	584.0
					240	P	65.5				3.5		
					240	WB	62.4	16.4	76.0	86.0		240	360.0

TABLE 1 (*continued*)

Case number	Age	Weight	Molar sodium *r*-lactate		Blood							Urine	
			Dose and diluent *	Per kgm. of body weight	Minutes after injection	Type of blood sample †	CO_2 content	Lactic acid	Glucose		Inorganic phosphorus	Minutes after injection ‡	CO_2 content
									True	Apparent			
	years	*kgm.*	*cc.*	*cc.*			*volumes per cent*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		*volumes per cent*
G-1982	6	15.0	70	4.7	0	S	63.0	21.4		99.0			
			+		15	S	77.5	65.6		90.0			
			210 W		30	S	93.4	46.7		90.0			
					60	S	80.0	41.7		82.0			
					120	S	60.0	31.5		90.0			
F-2131	8	22.7	170	7.5	0	WB	40.8	22.6	76.0	83.0		0	240.0
			+		30	WB	63.6	32.4	93.0	95.0			
			200 R		60	WB	61.0	18.0	79.0	90.0		60	308.0
					120	WB	59.9	15.1	85.0	90.0		120	254.0
					240	WB	59.4	17.6	90.0	103.0		240	241.0
H-925	12	35.5	240	6.8	0	P	57.6						
			+		0	WB		26.5	63.0	58.0?	2.9	0	22.1
			250 R		30	P	70.0						
					30	WB		60.0	76.0	89.0	2.8	30	99.6
					60	P	86.0						
					60	WB		51.0	67.0	80.0	2.5	105	311.0
					120	P	84.3						
					120	WB		25.5	114.0	124.0	2.5		
					240	P	82.8						
												240	498.0

* Diluent = Ringer's solution (R) or distilled water (W).

† S = Serum
WB = Oxalated whole blood
P = Oxalated plasma

‡ Indicates the end of the interval during which urine was collected.

chiefly to the metabolism of the lactate radicle, as indicated by the behavior of glucose and bicarbonate.

Blood glucose. During the first half hour after the intravenous injection of sodium *r*-lactate the glucose concentration rises, the average greatest increase of "true" glucose during this time being 20 mgm. per 100 cc. (Case G-1982, Table 1, is excluded as no "true" glucose values were determined.) During the second half hour its concentration either remains stationary or begins to fall. During the second hour a fall usually occurs and a level approximating the initial concentration is usually reached. Later there is a distinct tendency to rise.

The "true" glucose values were estimated by precipitating the blood proteins with the zinc sulphate reagent of Somogyi (7) and determining the reducing value of the filtrate with the Shaffer-Hartmann reagent (8) in its original form or as modified by Scharles and West (9). The "apparent" glucose values were determined by the original Shaffer-Hartmann procedure (8). Lactate itself in the concentration present during these studies, has no reducing effect on either reagent.

In general the "true" and "apparent" glucose values fluctuate in a parallel fashion.

Blood inorganic phosphate. Inorganic phosphate was followed in only two instances (Case G-336 and Case H-925, Table 1). A slight fall was noted during the first half hour, which became more rapid during the second half hour, after which in Case G-336 there was a continued rise. In neither instance had the original concentration been reached four hours after injection.

Blood carbon dioxide content. The carbon dioxide content of whole oxalated blood rises in a fashion similar to the increase of "true" glucose. The peak is reached usually at the end of the second half hour, although in two instances, Cases G-2078 and G-1982 (Table 1) the highest value was noted at the end of the first half hour. During the second hour and the subsequent two hours the concentration falls steadily, due largely to excretion of bicarbonate into the urine. The concentration at the end of four hours is not always as low as the initial concentration, but is usually within the upper range of normal. The serum and plasma carbon dioxide content values (Case G-336, Table 1) almost parallel the whole blood values, the curves diverging a little as the values increase and converging as they later decrease—in all probability a Donnan equilibrium effect, secondary to increasing and decreasing alkalinity.

Carbon dioxide content of the urine. The carbon dioxide content of the urine begins to rise at almost the same time that the carbon dioxide content of the blood rises. The greatest concentration usually appears after about one hour. The highest value was observed in Case G-336, Table 1. During the second hour the carbon dioxide content was 584 volumes per cent, representing a concentration of sodium bicarbonate of approximately 21.5 grams per liter.

DISCUSSION

From the above results it would seem that under normal conditions the intravenous injection of molar sodium *r*-lactate solution in a dose of from 4 to 7 cc. per kilogram of body weight is followed by practically complete utilization of the lactic acid during the period of two hours following the injection. The maximal amount, if injected uniformly over a period of 30 minutes, would correspond to the injection of *d*- and *l*-lactic acid at a rate of 0.63 gram of each per kilogram per hour. If all of the lactate is metabolized, as is indicated by the small amount excreted into the urine and by the extent of increase of bicarbonate in the blood, one would expect from the work of Meyerhof and Lohmann (10) and Cori and Cori (11) and their associates that about 80 per cent of the *d*-lactate (corresponding to 0.5 gram of lactic acid per kilogram per hour) would be converted into liver glycogen, while all of the *l*-lactate together with 20 per cent of the *d*-lactate (corresponding to 0.76 gram of lactic acid per kilogram per hour) would be oxidized. The heat production for this amount of lactic acid oxidation would correspond to about 3 calories per kilogram per hour, approximately double the basal metabolic rate of normal children.

If we assume that two-thirds of the body weight represents the weight of body water in equilibrium with and including the blood, we can calculate the expected increase in carbon dioxide content quite readily. Thus, if a subject receives 6.7 cc. of molar sodium *r*-lactate per kilogram of body weight, there should be an increase of 10 cc. of molar sodium bicarbonate per kilogram of body water, equivalent to an increase in carbon dioxide content of approximately 22.4 volumes per cent. In Table 2 the expected

TABLE 2

Effect of intravenous administration of sodium r-lactate on the CO_2 content of whole blood of normal human subjects

History number	Age	Body weight	Body water	Molar sodium lactate	CO_2 content			Difference
					Before	After 1 hour	Expected	
	years	*kgm.*	*liters*	*cc.*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*
G-2078	5	18.5	12.4	130	48.5	67.6	75.6	− 10.3
G-1982	6	15.0	10.0	70	63.0*	80.0*	78.7	+ 1.3
F-2131	8	22.7	15.2	170	49.8	61.0	74.9	− 13.9
G-2114	9	27.3	18.2	110	53.7	58.6	67.2	− 8.6
G-2155	12	33.9	22.7	140	54.7	64.5	68.5	− 4.0
G-336	14	42.6	28.6	245	51.1	66.6	70.3	− 3.7
"	"	42.6	28.6	245	56.4*	75.9*	75.6	+ 0.3
H-925	12	35.5	23.7	240	57.6	86.0	80.3	+ 5.7
							Average	= − 4.2

* Determinations on serum.

increase in carbon dioxide content of the blood is compared with that actually observed after one hour. It should be noted that in all instances but two the actually observed carbon dioxide content was less than that predicted, and that the average discrepancy was 4.2 volumes per cent. The chief reason for this discrepancy undoubtedly is the fact that considerable base, chiefly as bicarbonate, is excreted into the urine during the first hour. In Case G-336 during the initial hour the carbon dioxide content of the urine rose from 3.1 to 350 volumes per cent. The quantity of urine secreted during the interval was 100 cc. accounting for the excretion of approximately 15.5 cc. of molar sodium bicarbonate. As the subject had approximately 28.6 kilograms of body water, the loss of 15.5 cc. of molar sodium bicarbonate would cause a reduction in the carbon dioxide content of the entire body water of 1.21 volumes per cent. The difference originally to be accounted for in this instance was 3.7 volumes per cent. Undoubtedly, additional base (sodium) was excreted with other anions, such as chloride and sulphate.

The most alkaline urine observed in this study was noted during the second hour in this same subject. During this period, 150 cc. of urine with a carbon dioxide content of 584 volumes per cent were secreted, representing a concentration of sodium bicarbonate of approximately 21.5 grams per liter. In no instance was any clinical evidence of alkalosis, such as tetany, noted despite the fact that in one instance (Case G-1982 Table 1) a serum carbon dioxide content of 93.4 volumes per cent resulted. In all probability the respiratory response was sufficient to prevent any significant shift in pH.

SUMMARY AND CONCLUSIONS

In seven essentially normal children the effects of the intravenous injection of from 4 to 7 cc. of molar sodium *r*-lactate per kilogram of body weight were studied, with the following results:

1. The racemic mixture is practically completely metabolized in from one to two hours.

2. The conversion of lactate into glucose is apparent from the uniform rise of the latter in the blood.

3. The liberation of the sodium ion is practically quantitative, the base appearing in the body fluids chiefly as sodium bicarbonate.

4. Excretion of excess base into the urine takes place promptly, and alkalosis is usually of short duration.

5. During the duration of alkalosis no signs of tetany were noted.

BIBLIOGRAPHY

1. 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.

2. 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. II. Acute Hemorrhagic Nephritis. Sub-Acute Nephritis; Severe Chronic Nephritis.
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.
4. Cunningham, R. D. M., and Darrow, D. C., Am. J. Dis. Child., 1931, xli, 1347. Preparation of a Solution of Sodium Bicarbonate and Sodium Chloride for Hypodermoclysis.
5. Hartmann, A. F., and Elman, R., J. Exp. Med., 1929, 1, 387. The Effects of Loss of Gastric and Pancreatic Secretions and the Methods for Restoration of Normal Conditions in the Body.
6. Hartmann, A. F., and Smyth, F. S., Am. J. Dis. Child., 1926, xxxii, 1. Chemical Changes in the Body Occurring as the Result of Vomiting.
7. Somogyi, M., Proc. Soc. Exp. Biol. and Med., 1929, xxvi, 353. A Method for the Preparation of Blood Filtrates for Analysis.
8. Shaffer, P. A., and Hartmann, A. F., J. Biol. Chem., 1921, xlv, 349 and 365. The Iodometric Determination of Copper and Its Use in Sugar Analysis. I. Equilibria in the Reaction Between Copper Sulfate and Potassium Iodide. II. Methods for the Determination of Reducing Sugars in Blood, Urine, Milk and Other Solutions.
9. Scharles, F. H., and West, E. S., J. Biol. Chem., 1931, xciii, 359. The Combined Sugar of Tungstic Acid Filtrates of Blood.
10. Myerhof, O., and Lohmann, K., Biochem. Ztschr., 1926, clxxi, 421. Über Atmung und Kohlehydratumsatz tierischer Gewebe. III. Über den Unterschied von d- und l-Milchsäure für Atmung und Kohlehydratsynthese im Organismus.
11. Cori, C. F., and Cori, G. T., J. Biol. Chem., 1929, lxxxi, 389. Glycogen Formation in the Liver from *d*- and *l*-Lactic Acid.