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The Metabolic Acidosis Resulting from Intravenous Tetracycline Administration (37829)

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An overwhelming metabolic acidosis following intraperitoneal administration of toxic doses of tetracycline to rats was observed by Greenberger *et al.* (1). The nature of the acidosis, however, was not determined. It has been suggested (2) that a lactic acidosis might be a universal finding in tetracycline toxicity if patients were screened for a lactic acidosis. Lactic acidosis has been reported in four patients with fatty livers occurring after intravenous administration of tetracycline (2, 3).

The present study was undertaken to determine the cause of the metabolic acidosis associated with tetracycline administration and specifically to determine if the anion associated with the acidosis was indeed lactate. Our results do not substantiate the suggestion that lactic acidosis always is associated with tetracycline toxicity.

Materials and Methods. Five groups of animals, five adult mongrel dogs per group, were studied. Group I received a commercial iv tetracycline–HCl preparation (Tet HCl iv prep.) (Tetracyn Intravenous[1]), 300 mg/kg body wt. This preparation contains 1.5 g ascorbic acid/500 mg tetracycline–HCl. Group II received pure tetracycline–HCl[2] (Tet HCl), 300 mg/kg body wt. Group III received the same iv preparation (Tet HCl iv prep.) and dosage as Group I, but this was followed immediately by infusion of tromethamine[3] (THAM) in an amount calculated to neutralize the acids (ascorbic plus HCl) present in the dose administered. Group IV received hydrochloric acid equivalent to that given in Groups I, II, and III. Group V received ascorbic acid equivalent to that given in Groups I and III. The calculated dose of each medication, dissolved in 5% dextrose in water, was given in a volume of 30 ml/kg body wt. This solution was administered over a period of 45–60 min via a catheter in the right femoral vein which was threaded into the inferior vena cava.

Prior to the drug infusion, the dogs were anesthetized with iv sodium pentobarbital, 15 mg/kg body wt. An endotracheal tube was inserted and animals were ventilated with room air using a Harvard respirator. A catheter was placed in the abdominal aorta by way of the left femoral artery for collection of blood samples and recording pressure. Arterial blood samples were obtained prior to administration of the drug, at the end of the drug infusion, hourly thereafter for 4 hr, and at 24 hr in the survivors. Arterial pH, PCO_2, PO_2, and HCO_3^- concentration were determined using an Instrumentation Laboratories blood gas apparatus and the base excess calculated. Oxygen hemoglobin saturation was determined using an American Optical Oximeter. Serum electrolytes were performed in the clinical chemistry laboratory. Blood lactate levels were

[1] Registered trademark, J. B. Roerig Division, Charles Pfizer and Co., Inc., New York, NY 10017.

[2] Kindly supplied by the Upjohn Company, Kalamazoo, MI 49001.

[3] Obtained from Abbott Laboratories, North Chicago, IL 60064.

measured by our modification (4) of the Barker and Summerson method (5), pyruvate by the Huckabee modification (6) of the Friedemann and Haugen method, ascorbic acid by the method of Roe (7), and ketone bodies by the method of Chernick (8). The electrocardiogram and blood pressure were monitored through the 4-hr sample. Statistical analysis was preformed by our computer center.

Results. In the animals receiving tetracycline, none survived for 24 hr in Group I, 3 survived in Group II, and 1 in Group III. Of the dogs that did not receive tetracycline, Groups IV and V, all survived for 24 hr following the infusion of either HCl or ascorbic acid.

A marked bradycardia with a prolongation of the Q–T interval and a moderate hypotension were observed in all animals receiving tetracycline whereas no change in heart rate or blood pressure was noted in Groups IV and V. PCO_2, PO_2, and oxygen hemoglobin saturation were within normal limits throughout the experiment in all groups.

Data on changes in pH, blood gases, and serum electrolytes are shown in Table I. There were no significant changes in levels of Na^+, Cl^-, and K^+. Serum Ca^{2+} was markedly decreased by tetracycline. All animals had a decrease in arterial pH and a moderate to severe metabolic acidosis. This could not be corrected for, except temporarily by THAM, as seen in Group III. Blood levels of lactic and pyruvic acids rose significantly but not to the high levels seen in hemorrhagic shock or reported in patients with tetracycline toxicity (2, 3). Excess lactate levels were either near zero or were of a negative value. Ascorbic acid levels were unchanged in dogs not receiving this drug but markedly elevated in Groups I, III, and V, gradually returning toward normal levels after 24 hr in the survivors. Ketone body levels were determined in Groups I and V only and were normal or only slightly elevated but not enough to account for any measurable amount of the acidosis observed.

A graphic representation of the base deficit of the average of each group is shown in Fig. 1. In all groups the base deficit is great-

TABLE I. Effect of an Intravenous Tetracycline Preparation and Its Equivalent Components on Blood pH, Base Excess, and Serum Ca^{2+} Levels.

	Tet HCl iv prep.			Tet HCl			Tet HCl iv prep. + THAM			Ascorbic acid[a]			HCl[a]	
	pH	Base excess (mEq/liter)	Ca^{2+} (mg%)	pH	Base excess (mEq/liter)	Ca^{2+} (mg%)	pH	Base excess (mEq/liter)	Ca^{2+} (mg%)	pH	Base excess (mEq/liter)		pH	Base excess (mEq/liter)
Control	7.39	— 1.2	9.4	7.41	— 2.1	9.5	7.40	— 2.6	9.8	7.40	— 1.0		7.40	—4.1
End Inf.	6.87*	—25.5*	5.4*	7.22*	—12.4*	4.9*	6.91*	—26.2*	5.3*	7.10*	—17.8*		7.30*	—8.9*
+ THAM							7.36	— 6.3	5.8*					
1 hr	7.04*	—20.8*	7.9*	7.24*	—11.7*	6.4*	7.28*	— 9.5*	7.2*	7.21*	—13.1*		7.31	—8.6
2 hr	7.05*	—20.3*	8.0*	7.24*	—11.8*	7.1*	7.28*	— 9.9*	7.8*	7.25*	—11.1*		7.31	—8.3
3 hr	7.06*	—19.6*	8.2*	7.24*	—13.0*	7.5*	7.31*	—11.6*	7.8*	7.27*	—10.2*		7.35	—7.9
4 hr	7.08*	—19.5*	8.3*	7.24*	—13.1*	7.9*	7.31*	—11.7*	7.9*	7.30	— 8.7*		7.37	—7.5
24 hr				7.19*,[b]	—16.1*,[b]	7.9*,[b]				7.36	— 6.0		7.41	—3.4

[a] Ca^{2+} levels remained unchanged in these groups.

[b] 3 animals survived 24 hr.

* Values are significantly different from the control value of that group ($P < .05$).

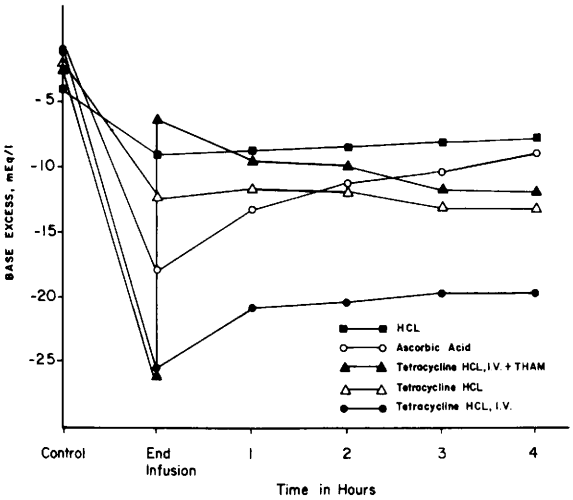

FIG. 1. The base deficit occurring in dogs receiving a commercial iv tetracycline preparation (300 mg/kg body wt) and its equivalent individual components.

est at the end of the infusion and gradually returns toward normal over the next 4 hr. Animals receiving tetracycline (Groups I, II, and III) show the least return toward normal. In Fig. 2, the base excess from the end of the infusion through the 4-hr sample for Groups I, II, and III is corrected for the control level and replotted from Fig. 1, as is the base excess from the combined Groups IV and V similarly corrected. In Fig. 2 is also plotted the combined milliequivalents of lactate and pyruvate from Table II again corrected for their control levels. It is evident from Fig. 2 that the metabolic acidosis from the infusion of tetracycline has a component which cannot be explained by the combined acidosis of that produced by ascorbic acid alone plus hydrochloric acid alone plus the lactate and pyruvate.

Discussion. When the study of Greenberger *et al.* (1) was repeated in our laboratory using rats, serial blood samples from the tail vein were unobtainable, suggesting that these animals had a marked vasoconstriction as if in a state of shock. Therefore dogs were employed in this study. The production of a marked bradycardia combined with a moderate fall in arterial blood pressure should result in poor tissue perfusion. By this mechanism a rise in lactate level and the development of excess lactate would be expected. Since this did not develop in our study, the high lactate levels reported in patients (2, 3) would not appear to be a direct result of the tetracycline administration.

The consistent but not always large negative excess lactate was an unexpected finding in animals receiving tetracycline. This is an exceedingly rare occurrence in our experience during open heart surgery (9) and has not been reported, at least in these levels, in the literature. For this to occur, the level of pyruvate rose to a much larger extent than lactate, suggesting that tetracycline blocks the conversion of pyruvate to lactate. This may be due to a direct effect of tetracycline on the enzyme lactic dehydrogenase, and studies are in progress to evaluate this suggestion. An alternate explanation would involve inhibition of synthesis of the enzyme, since inhibition of protein synthesis by tetracycline has been demonstrated (10). The inhibition of synthesis appears unlikely because of the rapidity in which the changes in negative excess lactate occur and its nonprogressive nature with time.

In our study, the administration of ascorbic acid alone or HCl alone produced a definite metabolic acidosis which is directly opposite the findings of Greenberger *et al.* (1) in rats. This was not unexpected since an acidosis has been reported both with HCl administration in dogs (11) and with ascorbic acid in rats (12). When the level

TABLE II. Effect of an Intravenous Tetracycline Preparation and Its Equivalent Components on Blood Lactate, Pyruvate, Excess Lactate, and Ascorbic Acid Levels.

	Tet HCl iv prep.				Tet HCl			Tet HCl iv prep. + THAM[a]			Ascorbic acid[a]			HCl[a]	
	Lactate (mM)[c]	Pyruvate (μM)[c]	Excess lactate (mM)[c]	Ascorbic acid (mg%)	Lactate (mM)[c]	Pyruvate (μM)[c]	Excess lactate (μM)[c]	Lactate (mM)[c]	Pyruvate (μM)[c]	Ascorbic acid (mg%)	Lactate (mM)[c]	Pyruvate (μM)[c]	Ascorbic acid (mg%)	Lactate (mM)[c]	Pyruvate (μM)[c]
Control	1.27	75		0.9	1.46	79		1.17	88	0.9	1.17	69	0.9	1.98	102
End Inf.	1.96	127*	—0.32	154.5*	2.39*	193*	—1.23*	1.47	162	210.2*	1.15	75	124.6*	2.87	188
+ THAM								3.56*	314*	141.7*					
1 hr	2.37*	204*	—0.88*	102.1*	3.12*	295*	—2.51*	3.16*	348*	91.6*	1.29	98	54.8*	3.47	243
2 hr	2.46*	218*	—1.25*	74.3*	3.41*	356*	—3.11*	3.40*	447*	66.4*	1.26	108	41.5*	2.97	242
3 hr	2.32	221*	—1.42*	63.9*	3.29*	336*	—2.85*	3.72*	385*	57.1*	1.08	91	26.7*	3.30	208
4 hr	2.67*	212	—0.82*	51.7*	3.31*	304*	—2.12*	4.17*	469*	48.7*	0.97	82	19.7*	3.09	208
24 hr					3.05*,[b]	327*,[b]	—3.94*,[b]				1.35	116*	5.0	1.71	121

[a] Excess lactate values were all negative in these groups but were not significant from zero.

[b] 3 animals survived 24 hr.

[c] Concentration per liter.

* Values are significantly different from the control value of that group ($P < 0.05$).

of acidosis (base deficit) measured in animals receiving tetracycline is corrected for that produced by the combined ascorbic and hydrochloric acids given alone (Fig. 2),

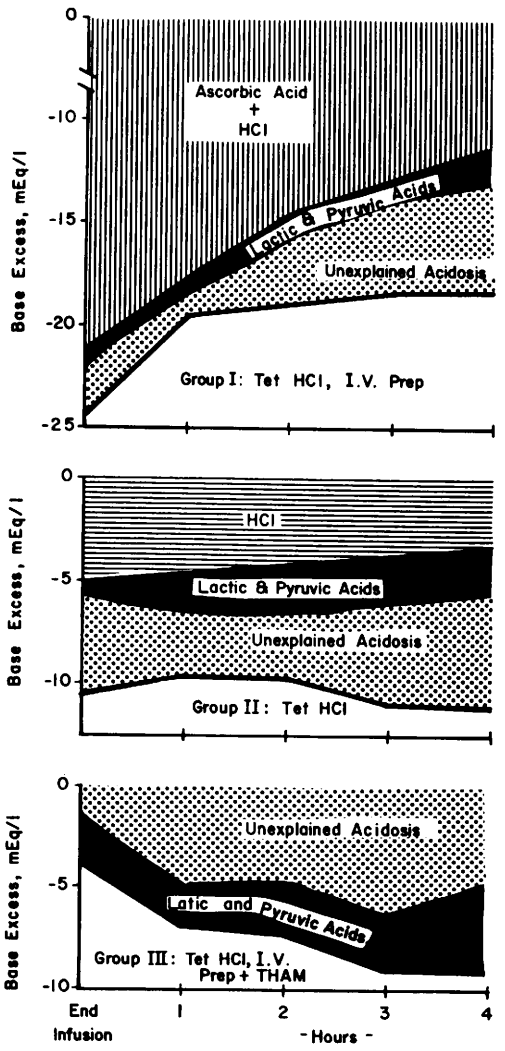

Figure 2. Components of the Acidosis following Intravenous Tetracycline.

Acidosis Attributable to Ascorbic and Hydrochloric Acids

Acidosis Attributable to Hydrochloric Acid

Acidosis Attributable to Lactic and Pyruvic Acids

The Unexplained Acidosis

The Base Deficit of the Tetracycline Preparation Administered Corrected for the Control Level

there still remains a considerable amount of base deficit which is unexplained by other anions, i.e., lactate, pyruvate, and ketone bodies, and may be due to a direct effect of the tetracycline. This suggestion is substantiated by the animals in Group III in which the acidosis at the end of the tetracycline infusion was corrected by buffering with THAM. In this group there was still an unexplained base deficit at 4 hr.

The reported hyperkalemia in rats (1) failed to develop in the dogs in this study. In the three groups of dogs receiving different tetracycline preparations, there was a slight fall in serum potassium levels in two groups and a slight rise in the third group, but these changes were not significant at the 5% level. These results were also supported by continuous electrocardiographic recordings in which no evidence of hyperkalemia (cardiac arrhythmias) was observed in the first 5 hr after beginning the tetracycline administration. We cannot rule out the possibility that cardiac arrhythmias were a late development.

The mechanism of the fall in blood calcium levels was not determined. The prolongation of the Q–T interval in the electrocardiogram is consistent with the observed hypocalcemia. It has been shown that calcium ions do complex with tetracycline (13) and could move with the tetracycline into tissues. It has also been suggested that calcium moves into damaged cells such as the liver cell in the fatty liver from tetracycline toxicity (14).

The failure to find high levels of lactic acid (12–20 mEq/liter) as reported in patients with fatty livers from tetracycline toxicity would seem to indicate that a lactic acidosis is not a constant finding with toxic levels of tetracycline. The lactic acidemia in these patients may be the result of other causes and not a direct effect of the drug. It appears, however, that tetracycline does have a direct effect in producing a metabolic acidosis which cannot be accounted for by some of the more usual organic acids found in blood, i.e., lactic, pyruvic, acetoacetic, or β-hydroxybutyric acids.

Summary. The metabolic acidosis resulting from acute toxic doses of parenterial

tetracycline was studied in dogs and compared to the acidosis produced by equivalent amounts of ascorbic acid and HCl found in the parenterial preparations. A severe metabolic acidosis developed which could be only partially corrected by buffering with THAM. A large portion of the acidosis could not be accounted for by lactic, pyruvic, or metabolites of ascorbic acid.

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