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Bicarbonate osmolality
body water THAM
extracellular fluid

Osmotic Effects of Infusion of THAM

WILLIAM C. HEIRD[20], RALPH B. DELL, TREVOR PRICE, AND ROBERT W. WINTERS

Department of Pediatrics, College of Physicians and Surgeons of Columbia University, New York, New York, USA

Extract

Changes in plasma osmolality as well as in extracellular fluid (ECF) space following infusion of THAM or $NaHCO_3$ to anesthetized, nephrectomized dogs have been used to compare the osmotic effects of the two agents. Groups of five to six dogs received (per kg body weight) 10 millimoles THAM (pH 7.3), 10 millimoles THAM (pH 8.5), 5 millimoles $NaHCO_3$, 10 millimoles $NaHCO_3$ or 5 millimoles NaCl, while a control group of five dogs received no infusion. Increases in plasma osmolality and ^{36}Cl space (ECF) were greater following infusion of THAM (pH 7.3 or pH 8.5) than after infusion of either $NaHCO_3$ or NaCl. Specifically, the osmotic effects of THAM, as judged from increases in osmolality of the body fluids and in ^{36}Cl space, were much greater than those of a 5-millimole dose of $NaHCO_3$, which produced an equivalent rise in plasma bicarbonate, and were even greater than those of an equimolar dose of $NaHCO_3$ (10 millimoles/kg). Furthermore, the increase in concentration of plasma bicarbonate produced by this dose of $NaHCO_3$ was much greater than that produced by THAM. Although theoretical considerations have predicted that the osmotic effects of THAM would be as great or greater than those of $NaHCO_3$, this is the first experimental documentation.

Speculation

The results reported herein provide further evidence for the view that THAM is not superior to $NaHCO_3$ for treatment of clinical acid-base disturbances.

Introduction

Tris (hydroxymethyl) aminomethane, or THAM, has been advocated as a more effective alkalinizing agent than bicarbonate or lactate for the treatment of clinical states of acidosis, particularly respiratory acidosis. This view is based in part upon the fact that THAM, in contrast to other buffers, can neutralize carbonic acid and thus lower the CO_2 tension of such patients [12]. In addition, the facts that THAM is a stronger base than bicarbonate (pK′ 7.84 *versus* 6.10) and that it allegedly enters cells more rapidly than bicarbonate [8, 11] have been proffered as further evidence of its superiority. Finally, since THAM contains no sodium, it has been argued that THAM would exert fewer osmotic effects than would the sodium-containing buffers and thus it would be particularly advantageous for use in patients in whom the administration of sodium is undesirable [9].

These points attesting to the superiority of THAM as an *in vivo* buffer have been challenged on theoretical and experimental grounds. They have been discussed extensively by Bleich and Schwartz [2], and all points except the last have been adequately negated. The purpose of this study was to test the contention that THAM exerts fewer osmotic effects than do sodium-containing buffers and thereby minimizes internal redistribution of total body water (TBW).

Materials and Methods

Mongrel dogs weighing 9–12 kg were anesthetized with sodium pentobarbital (30 mg/kg body weight), intubated, given succinylcholine (as necessary to maintain paralysis of the respiratory muscles) and ventilated with a variable rate and volume respiratory pump. End tidal CO_2 was maintained at a value which maintained Pa_{CO_2} constant at approximately 40 mm Hg. Catheters were placed in the femoral artery (for blood sampling and for monitoring of blood pressure) and in the femoral vein (for administration of infusions). Ligatures were placed about the splenic and renal pedicles through a midline abdominal incision in order to prevent changes in blood volume during the experiment and to prevent excretion of isotopes and other infused agents as well as renal acid-base adjustments.

Group I (five dogs) received 10 millimoles/kg body weight of a 4 M solution of THAM titrated with HCl to pH 8.5, the pH of the commercial preparation. Highly concentrated solution was used to minimize the water load incident to the infusion. As an osmotic control (*i.e.*, without acid-base effect), *Group II* (six dogs) received 10 millimoles/kg body weight of 4 M THAM titrated with HCl to pH 7.33—the mean pH of the nephrectomized control animals when maintained at a Pa_{CO_2} of 40 mm Hg. To compare the osmotic effects of THAM infused at pH 8.5 with an amount of $NaHCO_3$ yielding similar acid-base effects, *Group III* (six dogs) received 5 millimoles of 1 M $NaHCO_3$ per kilogram. *Group IV* (five dogs) received 10 millimoles of 1 M $NaHCO_3$ per kilogram in order to compare the effects of equimolar amounts of $NaHCO_3$ and THAM. *Group V* (five dogs) received 5 millimoles of 4 M NaCl per kilogram, and thus served as a further osmotic control. *Group VI* (six dogs) received no infusion. *Group VII* (six dogs), like Group I, received 10 millimoles/kg of 4 M THAM at pH 8.5; in this group, however, ECF volume was estimated from the volume of distribution of ^{14}C-inulin rather than ^{36}Cl.

Figure 1 shows the results obtained in a single animal in Group I and serves to illustrate the experimental design. Ninety to 120 min before infusion of the osmotic agent to be studied (*i.e.*, THAM, $NaHCO_3$, etc.), tritiated water (THO) and ^{36}Cl were injected; 20 min before the osmotic infusion, ^{51}Cr-tagged erythrocytes were injected. Control blood samples for the necessary analyses (see below) were obtained just prior to the infusion. The infusion required 10–20 min, the end of which was designated time 0. Blood samples were obtained at 30, 60, 90, 120, 180, and 300 min thereafter. Whole blood samples were counted for ^{51}Cr, and the concentrations of ^{36}Cl and THO in plasma were determined [5]. Concentrations of Na^+,

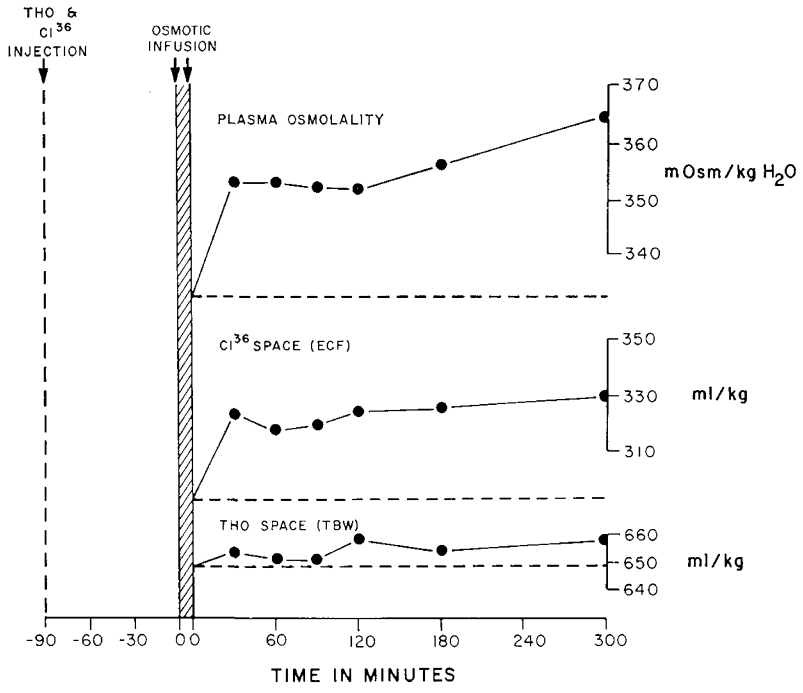

Fig. 1. Experimental design. *ECF:* extracellular fluid. *TBW:* total body water.

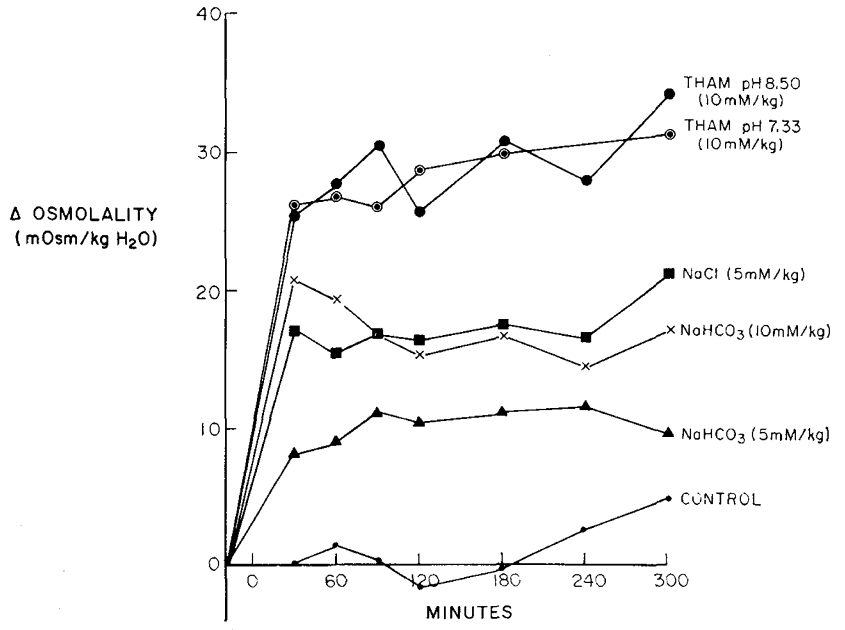

Fig. 2. Increase in osmolality following infusion of THAM, $NaHCO_3$, or NaCl.

K^+, Cl^-, glucose, and urea in plasma as well as blood acid-base status were determined in duplicate for each sample [1, 4]. Plasma osmolality was determined by freezing point depression with an osmometer [16].

Throughout the experiment, small amounts of 0.9% NaCl were given to maintain patency of the catheters as well as for administration of succinylcholine; the total volume of the infusions over the entire 5-hr period was never more than 30 ml/kg body weight.

Results

Figure 2 depicts the mean increase in plasma osmolality observed in all groups of animals during the experiment (*Groups I* and *VII* are combined in this figure). It is obvious that the rise in osmolality was greatest in those animals which received THAM of either pH. A significantly smaller rise in osmolality was observed in the animals which were given 5 millimoles of NaCl per kilogram body weight or either dose of $NaHCO_3$. Small rises in osmolality occurred in nearly all groups near the end of the experiment; these were attributable in part to the observed increases in concentrations of urea, Na^+ and Cl^-, the latter being incident to the small infusions necessary to maintain catheter patency.

Table I shows the mean changes in TBW and ECF observed in each of the seven groups. The total body water increased slightly (15–20 ml/kg) in all experiments due to accumulation of the small amounts of fluid used to maintain patency of the catheter and to infuse necessary drugs. In each of the infused groups, ECF volume showed an abrupt increase which was maintained throughout the 5-hr period of study.

In order to estimate the effects of the administered osmotic load upon the increase in ECF volume, ECF volume was calculated as the percentage of TBW at each time period for each dog. The increase in this proportion for each time period was then calculated as a percentage change of the value observed at time 0. These values for all dogs in each group were averaged so that the final value represents the group mean of $(ECF_t/TBW_t)/(ECF_1/TBW_1)$. This calculation is tantamount to estimating the ratio of osmotic load as a proportion of total ECF solute to osmotic load as a proportion of total body solute (see *Appendix*). The calculated values are depicted in Figure 3. As would be expected from the changes in plasma osmolality, the increase in ECF volume induced by THAM infused at either pH 8.5 or pH 7.3 (*Groups I* and *II*) was significantly greater than that induced by any other agent. Animals which received $NaHCO_3$ (*Groups III* and *IV*) and those which received NaCl (*Group V*) had increases in ECF volume which were significantly larger than those observed in the controls (*Group VI*).

Table II shows the changes in plasma $[HCO_3^-]$ noted over the course of the experiment in each group. During the first 90–120 min, the increase in plasma $[HCO_3^-]$ produced by the infusion of 5 millimoles of

Table I. Volumes of total body water (TBW) and extracellular fluid (ECF) in each group of animals

Time, min	*Group I:* THAM, pH 8.5, 10 millimoles/kg		*Group II:* THAM, pH 7.3, 10 millimoles/kg		*Group III:* $NaHCO_3$, 5 millimoles/kg		*Group IV:* $NaHCO_3$, 10 millimoles/kg		*Group V:* NaCl, 5 millimoles/kg		*Group VI:* control		*Group VII:* THAM, pH 8.5, 10 millimoles/kg	
	TBW[1]	ECF[2]	TBW	ECF	TBW	ECF	TBW	ECF	TBW	ECF	TBW	ECF	TBW	ECF
0	648	294	638	264	636	266	655	276	592	250	661	282	628	170
30	654	325	642	301	649	285	660	302	598	265	673	287	631	196
60	652	319	648	304	649	286	665	302	597	264	672	289	639	192
90	651	320	646	304	649	284	666	302	597	263	674	293		
120	659	326	646	299	649	286	672	301	601	270	689	300	644	197
180	655	323	644	297	653	288	674	302	600	271	680	300	647	203
240					654	293	672	304	601	272	688	305	648	205
300	659	331	659	315	657	299	676	304	605	276	692	308	644	209

[1] TBW in milliliters per kilogram calculated from tritiated water space; standard deviation of the observations is 56.4 ml/kg. This standard deviation is the pooled standard deviation for each group and is the best estimate of the standard deviation for each value in the table.

[2] ECF in milliliters per kilogram calculated from ^{36}Cl space except for *Group VII* where ECF was calculated from ^{14}C-inulin space; standard deviation of the observation is 31.8 ml/kg.

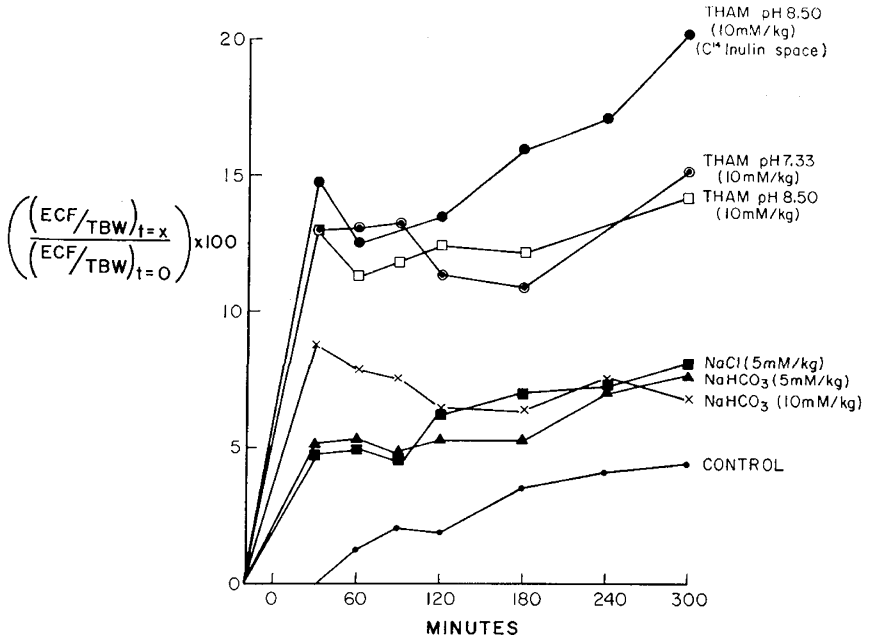

Fig. 3. Percentage increase in ratio of extracellular fluid (ECF) to total body water (TBW) following infusion of THAM, $NaHCO_3$, or NaCl.

$NaHCO_3$ per kilogram body weight (*Group III*) was nearly as great as that induced by 10 millimoles of THAM at pH 8.5 per kilogram (*Group I*) but only about one-half that observed after infusion of 10 millimoles of $NaHCO_3$ per kilogram (*Group IV*). After 120 min, plasma [HCO_3^-] tended to decrease in all groups of animals, which reflected acid accumulation incident to nephrectomy and general deterioration of the preparation. Changes in blood pH closely reflect those expected from observed changes in plasma [HCO_3^-] at a constant P_{CO_2}; these changes, as well as those which occurred in plasma [Na^+], are presented in Table III.

Discussion

The major purpose of this study was to determine whether THAM produces smaller increases in osmolality and ECF volume than does a comparable quantity of $NaHCO_3$. The results indicate that THAM causes a greater increase in osmolality of the body fluids as well as a larger percentage increase in ECF volume than does the dose of $NaHCO_3$ which produces an equivalent rise in plasma [HCO_3^-] (compare *Groups I* and *III*). Indeed, the increases in osmolality and ECF volume induced by THAM are even larger than those

induced by an equimolar amount of $NaHCO_3$ (compare *Groups I* and *IV*); the latter, however, causes a much larger increase in plasma $[HCO_3^-]$.

It is possible, by application of osmometric principles [14], to calculate the apparent osmotic load delivered to each group of animals studied (see *Appendix*). Table IV compares the calculated osmotic load received by each group with the osmotic load actually administered. It is somewhat difficult to calculate the osmotic load precisely because the osmotic consequences of the acid-base reactions undergone by both $NaHCO_3$ and THAM must be estimated. Thus, in determining the osmotic load actually delivered, two assumptions were made. *First*, that 40% of the infused bicarbonate ($NaHCO_3$) reacts with nonbicarbonate buffers to yield the conjugate base forms of the nonbicarbonate buffers (no net osmotic change) and H_2CO_3 [13]. The latter is eliminated as CO_2 so that only 60% of the infused bicarbonate remains as an osmotically active particle—*e.g.*, 10 millimoles of infused $NaHCO_3$ would yield 16 milliosmoles, 10 from Na^+ and 6 from HCO_3^-. *Second*, that at pH 8.5, 18% of the total amount of THAM is present as the chloride salt and so yields two osmotically active particles. Following infusion of THAM, the mean blood pH was 7.42, and at this pH THAM is 73% ionized. Consequently, 55% of the total THAM has reacted with weak acids (HBuf and H_2CO_3) to yield conjugate bases but only 60% of these are present as HCO_3^- (newly produced osmotic particles). Thus, 10 millimoles of THAM (pH 8.5) after administration yield 10 milliosmoles THAM, 1.8 milliosmoles Cl^- and 3.3 milliosmoles HCO_3^-, giving a total osmotic load of 15.1 milliosmoles. There is excellent agreement between the administered and the calculated osmotic loads at 60 min, which suggests that no unexpected factors contribute to the rise in osmolality observed after administration of any of the agents studied.

Table II. Variation of plasma bicarbonate concentration with time[1]

Time, min	*Group I:* THAM, pH 8.5, 10 millimoles/kg	*Group II:* THAM, pH 7.3, 10 millimoles/kg	*Group III:* $NaHCO_3$, 5 millimoles/kg	*Group IV:* $NaHCO_3$, 10 millimoles/kg	*Group V:* NaCl, 5 millimoles/kg	*Group VI:* control
0	18.8	19.0	17.5	18.4	18.6	20.3
30	27.8	19.1	29.2	37.5	19.3	20.7
60	27.5	18.9	27.5	36.7	19.5	21.0
90	27.7	18.8	27.2	36.2	19.7	20.6
120	26.4	18.0	26.2	35.0	19.4	20.9
180	24.5	16.6	25.8	34.4	19.0	20.0
240			25.0	32.4	17.7	20.3
300	19.1	15.7	23.3	31.7	17.4	19.3

[1] In milliequivalents per liter. Pooled standard deviation is 2.1 mEq/liter.

Table III. Variation of blood pH and concentration of sodium in plasma with time[1]

Time, min	*Group I:* THAM, pH 8.5, 10 millimoles/kg	*Group II:* THAM, pH 7.3, 10 millimoles/kg	*Group III:* $NaHCO_3$, 5 millimoles/kg	*Group IV:* $NaHCO_3$, 10 millimoles/kg	*Group V:* NaCl, 5 millimoles/kg	*Group VI:* control
			Blood pH[2]			
0	7.298	7.307	7.283	7.290	7.305	7.319
30	7.426	7.272	7.449	7.600	7.305	7.316
60	7.425	7.271	7.444	7.599	7.320	7.328
90	7.407	7.276	7.444	7.608	7.325	7.329
120	7.424	7.273	7.434	7.602	7.326	7.336
180	7.426	7.266	7.426	7.584	7.326	7.345
240			7.426	7.571	7.312	7.340
300	7.363	7.204	7.399	7.572	7.298	7.335
			Plasma $[Na^+]$[3]			
0	152.2	149.3	156.2	150.2	153.1	149.2
30	144.4	136.5	162.8	164.1	163.2	147.3
60	141.7	137.8	162.4	164.0	162.7	147.2
90	145.8	138.8	162.6	164.0	162.8	147.4
120	145.3	139.3	163.8	162.5	162.2	147.0
180	146.0	139.8	162.7	162.6	160.4	145.9
240			162.1	161.5	160.1	145.4
300	149.4	142.3	161.6	162.1	160.3	145.4

[1] Average of all values at each time period.

[2] Pooled standard deviation is 0.047.

[3] In milliequivalents per liter. Pooled standard deviation is 5.66 mEq/liter.

Table IV. Administered and calculated osmotic loads in the treated animals

	Group I: THAM, pH 8.5, 10 millimoles/kg	*Group II:* THAM, pH 7.3, 10 millimoles/kg	*Group III:* $NaHCO_3$, 5 millimoles/kg	*Group IV:* $NaHCO_3$, 10 millimoles/kg	*Group V:* NaCl, 5 millimoles/kg
Administered osmotic load, milliosmoles/kg[1]	15.10	17.70	8.00	16.00	10.00
Calculated osmotic load, milliosmoles/kg[2]	17.60	17.90	9.20	16.10	10.00
Mean ΔBE, mEq/liter[3]	9.5		11.9	21.20	
$\frac{\text{Calculated osmotic load}}{\text{Mean }\Delta\text{BE}}, \left(\frac{\text{milliosmoles}}{\text{mEq/liter}}\right) \Big/ \text{kg}$	1.85		0.77	0.76	

[1] Calculated as follows:

(*a*) *Group I* (final plasma pH 7.42; 1.51 milliosmoles/millimole infused):

$$HBuf + 0.82\ THAM + 0.18\ THAMCl \rightarrow 0.73\ THAM^+ + 0.18\ Cl^- + 0.33\ HCO_3^- + 0.22\ Buf^- + 0.27\ THAM$$

(*b*) *Group II* (final plasma pH 7.30; 1.77 milliosmoles/millimole infused):

$$0.23\ THAM + 0.77\ THAMCl \rightarrow 0.23\ THAM + 0.77\ THAM^+ + 0.77\ Cl^-$$

(*c*) *Groups III* and *IV* (1.6 milliosmoles/millimole infused):

$$NaHCO_3 + HBuf \rightarrow Na^+ + 0.6\ HCO_3^- + 0.4\ Buf^-$$

(*d*) *Group V* (2 milliosmoles/millimole infused):

$$NaCl \rightarrow Na^+ + Cl^-$$

[2] Calculated as follows (see *Appendix*): load = $TBW_1\Delta[Osm] + L_{H_2O}[Osm]$, where TBW is the total body water, [Osm] the osmolality, and L_{H_2O} the water given with the infused solute.

[3] ΔBE = base excess at 60 min minus control base excess.

The ratio of the osmotic load delivered to the available base delivered can be calculated for both THAM and $NaHCO_3$ from the data in Table IV and the mean change observed in blood base excess. After 60 min, the mean blood base excess had risen by 9.5 mEq/liter in the animals given THAM at pH 8.5 (*Group I*), whereas it had increased by 11.9 mEq/liter in those which received 5 millimoles of $NaHCO_3$ per kilogram body weight (*Group III*) and by 21.2 mEq/liter in those which received 10 millimoles $NaHCO_3$/kg (*Group IV*). The ratio of calculated osmotic load delivered to the mean increase in blood base excess for each group demonstrates clearly that for each milliequivalent rise in blood base excess, THAM delivers more than twice the osmotic load delivered by $NaHCO_3$.

It can be argued that, since THAM is excreted rapidly by the kidney, such an osmotic effect would not be seen in the intact patient. However, in a dog with intact, well perfused kidneys only 30–35% of an administered dose of THAM is excreted in 1 hr [10]. Furthermore, the percentage of THAM excreted by patients who usually require THAM—*i.e.*, patients with severe acid-base disturbances and concomitant reduction in glomerular filtration rate and urine flow—is likely to be less than that observed in normal dogs. The osmotic consequences after infusion of THAM or $NaHCO_3$ to dogs with intact kidneys are currently being investigated and will be the subject of a subsequent report.

It can also be argued that the rise in osmolality induced by THAM would have no effects upon internal distribution of body water if THAM, like urea, readily penetrated cells. On the other hand, if THAM were confined entirely to the ECF or entered cells only slowly, an increase in ECF volume would result. This could be of considerable importance, particularly in infants with respiratory distress syndrome or other such conditions associated with a compromised circulation. The observed data on changes in body fluid compartments (see Table I and Fig. 3) show that, although TBW remained relatively constant after THAM infusion, a sharp increase in ECF volume did, indeed, occur and that this increase was sustained throughout the 5-hr observation period.

The fact that ECF volume remains elevated after THAM administration has at least three explanations, and these are not necessarily mutually exclusive: (*a*) it is an artifact of equating the ^{36}Cl space with the ECF volume; (*b*) THAM enters cells by exchanging with some intracellular substance; (*c*) THAM enters cells very slowly.

The first explanation can be eliminated by the data from dogs of *Group VII* (Table I). These animals received 10 millimoles per kg body weight of THAM at pH 8.5, and the ECF volume was estimated by the volume of distribution of ^{14}C-inulin. The results (Fig. 3) indicate that, even when a radically different ECF marker is employed, ECF volume increases following THAM administration and remains elevated throughout the course of the experiment. Thus, the increases

in ^{36}Cl space observed in the other groups are more likely due to ECF volume expansion and not to an artifact of equating ^{36}Cl space with ECF volume.

There is some evidence for the second and third explanations. If THAM entered cells by exchanging with some intracellular substance, it should be possible to detect accumulation of this substance in the osmolar composition of the ECF. Therefore, calculated ECF osmoles were compared with measured ECF osmoles. Calculated osmoles at each time were determined by multiplying the osmotic concentrations of the measured contributors to extracellular osmolality (Na^+, K^+, Cl^-, HCO_3^-, urea, and glucose) by the respective ECF volume [15] and then summing the individual contributions at each time. The control or preinfusion calculated osmoles were then subtracted from the calculated osmoles at each postinfusion time, thereby giving the total increase in calculated ECF osmoles. These increases in total calculated ECF osmoles, expressed in milliosmoles per kilogram of body weight, are plotted in Figure 4. Also plotted are the increases in measured ECF osmoles at each time; these were calculated by multiplying the measured osmolality (determined by freezing depression) by the respective ECF volumes.

In the control animals (*bottom panel,* Fig. 4), there was a small but increasing discrepancy between calculated and measured osmoles. This suggests an accumulation, in nephrectomized animals, of a substance(s) other than those mentioned above. On the other hand, in both groups which received $NaHCO_3$ there was only slight (if any) discrepancy between the calculated and the measured osmoles, implying not only that most of the increase in osmolality was due to administered $NaHCO_3$ but also that maintenance of normal or elevated plasma bicarbonate concentration may reduce or eliminate the accumulation of the unknown substance(s) observed in the control group. In the dogs which received THAM, a discrepancy between the measured and calculated osmoles was also seen; it appeared early in the experiment and remained constant throughout. This discrepancy, which should represent the osmoles contributed by the THAM remaining in the ECF, was about 7 milliosmoles/kg body weight—approximately 30% less than the total THAM administered.

Studies of the kinetics of THAM distribution do not agree about the amount of THAM expected to remain in the ECF at various times following its administration. According to Holmdahl and Nahas [7], the discrepancy between calculated and measured extracellular osmoles that we have noted approximates the amount of THAM that would be expected to remain in the ECF up to 60 min after its administration. On the other hand, the discrepancy is somewhat greater than the amount that would be predicted from the studies of Robin *et al.* [11], but it is somewhat less than our unpublished kinetic data would suggest.

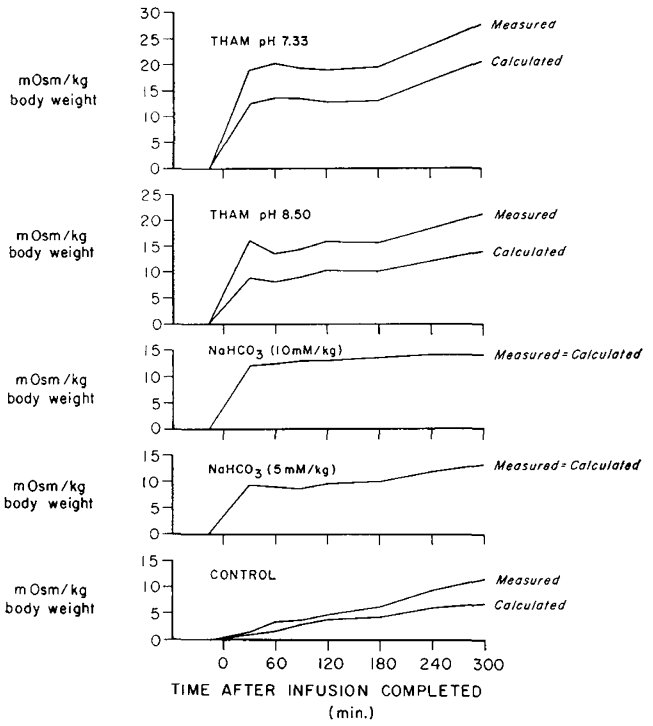

Fig. 4. Measured and calculated osmoles following administration of $NaHCO_3$ or THAM.

The fact that the discrepancy between calculated and measured osmoles in this study is less than the amount of THAM administered, together with the findings of the previously cited studies of the kinetics of THAM distribution [7, 11], indicates that THAM does leave the ECF, although at a rate which appears to vary from study to study. The constancy of the discrepancy noted between calculated and measured extracellular osmoles in this study—if this discrepancy truly represents the osmoles contributed by the THAM which remains in the ECF—suggests that little, if any, THAM enters the nonextracellular space except during the first 30 min after administration. This interpretation, however, is not consistent with previously reported studies [7, 11] or with our unpublished studies of the kinetics of THAM distribution. Alternatively, the constancy of the discrepancy between calculated and measured osmoles could be explained by an exchange between THAM and an intra-

cellular solute other than Na^+, K^+, Cl^-, HCO_3^-, or glucose so that the total ECF osmolality remains constant. Such an exchange need not be energy-linked or, for that matter, even related to the disappearance of THAM from the ECF. Indeed, accumulation in the ECF of the same substance(s) noted in control animals would easily explain the discrepancy.

It is obvious that the data reported here do not allow a precise interpretation of the discrepancy between calculated and measured ECF osmolality observed after THAM administration. However, animals in *Groups I* and *II* were given THAM labeled with ^{14}C which permitted determination of the apparent volume of distribution of ^{14}C-THAM. This only slowly approached the measured total body water; in fact, preliminary examination of the kinetics of THAM distribution indicates that it takes approximately 12–18 hr for THAM to equilibrate throughout the measured TBW—a far longer time than has previously been reported [7]. Whether there is an exchange process (related or unrelated) between THAM and another intracellular solute remains to be proven. Thus, it appears that THAM does enter cells but at a relatively slow rate. A thorough study of the kinetics of THAM distribution throughout TBW will be the subject of a forthcoming publication.

These experiments, then, indicate that THAM does not produce fewer osmotic effects than does $NaHCO_3$. In fact, for equivalent acid-base changes, THAM causes a greater increase in plasma osmolality than does $NaHCO_3$. Furthermore, since THAM penetrates cells relatively slowly, these osmotic effects are accompanied by a considerable increase in ECF volume which persists for some hours in nephrectomized dogs. Thus, these results provide further evidence for the view that THAM is not superior to $NaHCO_3$ for treatment of clinical acid-base disturbances.

Summary

The osmotic effects of THAM, as judged by increases induced in plasma osmolality and ECF (^{36}Cl) space of nephrectomized dogs, are somewhat greater than those of an equimolar amount of $NaHCO_3$. Furthermore, the increases in plasma [HCO_3^-] and in blood pH following $NaHCO_3$ administration are considerably greater than those induced by equimolar amounts of THAM, which indicates that, for equivalent acid-base changes, the osmotic effects of THAM far exceed those of $NaHCO_3$.

Appendix

Let: TBW = total body water in ml/kg
ECF = extracellular fluid volume in ml/kg
L_{osm} = osmotic load in milliosmoles/kg
L_{H_2O} = water load in ml/kg
osm = osmolality in milliosmoles/kg H_2O
TBS = total body solute in milliosmoles/kg
ECFS = extracellular fluid solute in milliosmoles/kg
Subscripts 1 and *2* refer to times before and after infusion, respectively.

If an osmotic load is confined to the ECF, then:

$$ECFS_1 + L_{osm} = ECFS_2 \tag{1}$$

or

$$ECF_1 \cdot osm_1 + L_{osm} = ECF_2 \cdot osm_2 \tag{2}$$

Similarly, for the total body water:

$$TBW_1 \cdot osm_1 + L_{osm} = TBW_2 \cdot osm_2 \tag{3}$$

Eliminating osm_2 between the two equations yields:

$$\frac{ECF_2}{TBW_2} = \frac{ECF_1 \cdot osm_1 + L_{osm}}{TBW_1 \cdot osm_1 + L_{osm}} = \frac{ECFS_1 + L_{osm}}{TBS_1 + L_{osm}} \tag{4}$$

At osmotic equilibrium the ratio of the volumes of ECF and TBW is given by the ratio of the solute in the ECF to the total body solute, or:

$$\frac{ECF_1}{TBW_1} = \frac{ECFS_1}{TBS_1} \tag{5}$$

Therefore:

$$\left(\frac{ECF_2}{TBW_2}\right) \Big/ \left(\frac{ECF_1}{TBW_1}\right) = \left(\frac{ECFS_1 + L_{osm}}{TBS_1\ L_{osm}}\right) \Big/ \left(\frac{ECFS_1}{TBS_1}\right) = \left(1 + \frac{L_{osm}}{ECFS_1}\right) \Big/ \left(1 + \frac{L_{osm}}{TBS_1}\right) \tag{6}$$

From equation (3) osmotic load may be calculated as:

$$\begin{aligned} L_{osm} &= TBW_2 \cdot osm_2 - TBW_1 \cdot osm_1 \\ &= (TBW_1 + L_{H_2O})osm_2 - TBW_1 \cdot osm \\ &= TBW_1 \cdot \Delta osm + L_{H_2O} \cdot osm_2 \end{aligned} \tag{7}$$

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15. Appropriate plasma water corrections, Donnan factors [3], and osmotic coefficients [6] were used in these calculations.
16. 3R Hi-Precision research osmometer, Advanced Instruments, Inc., Newton Highlands, Mass.
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20. Requests for reprints should be addressed to: WILLIAM C. HEIRD, M.D., Department of Pediatrics, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, N. Y. 10032 (USA).
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