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THE EFFECT IN HUMANS OF EXTRACELLULAR pH CHANGE ON THE RELATIONSHIP BETWEEN SERUM POTASSIUM CONCENTRATION AND INTRACELLULAR POTASSIUM¹

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For many years investigators have been aware of the association of hyperkalemia with acidosis and hypokalemia with alkalosis. The early *in vitro* work of Fenn and Cobb (1) suggested that there might be a cause and effect relationship. However, it was not until recently that satisfactory *in vivo* data were obtained (2-7) which permitted the formulation of the hypothesis that changes in extracellular pH altered the extracellular potassium concentration independently of changes in total body potassium³ (7). Thus, in animals, acidosis increases and alkalosis decreases the serum potassium concentration independently of changes in total body potassium. The present study demonstrates similar interrelationships in humans.

EXPERIMENTAL PLAN AND METHODS

Five patients were selected for study because of alterations of extracellular pH of either metabolic or respiratory origin. During the nine periods of study (five in the same patient) an attempt was made to change extracellular pH rapidly and observe the effect of this change on the serum potassium concentration. Extracellular pH was changed by appropriate therapy which included infusions of isotonic mixtures of NaCl, HCl, NH₄Cl, NaHCO₃ and sodium lactate. In one patient eight per cent CO₂ inhalation was used in combination with HCl infusion. In order to control the effect of changes in total body potassium on the serum potassium concentration experimental periods were short and an attempt was made to change potassium balance only slightly

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³ The effect of alterations of extracellular pH on the relationship between extracellular and intracellular potassium is probably related to intracellular buffering and therefore ultimately dependent upon intracellular pH change. However, since the latter cannot be measured, the relationship must be studied in terms of extracellular pH.

and in the direction opposite to the anticipated change in the serum potassium concentration. Because the caloric needs of none of the patients had been met during the periods antecedent to the experimental period, it was presumed that glycogen stores were depleted. During the experimental periods caloric needs were not met in order that potassium not be deposited with glycogen.

During the period of pH change sodium, potassium, chloride and nitrogen balances were determined in the usual manner. All patients were parenterally fed and none had stools during the period of study.

Femoral venous blood samples were considered to reflect more accurately than would arterial blood samples the pH of the extracellular space. Whole blood pH was determined anaerobically within ten minutes at 38° centigrade using a Cambridge pH meter with a glass electrode. Duplicate determinations, bracketed by standards, agreed within 0.02 pH unit. Sodium and potassium concentrations were determined by Baird internal standard flame photometry. Duplicate potassium determinations agreed within 0.1 mEq. per L. Chloride was determined by a modification of the Schales' mercury titration method (8). Plasma bicarbonate was determined by a modification of the Van Slyke titration (9). Serum and urine non-protein nitrogen was determined by the method of Koch and McMeekin (10).

Calculations

1. Change in the intracellular potassium content in excess of nitrogen,

$$\Delta K_I = bK' - \Delta K_E, \quad (1)$$

where:

bK' = Potassium balance corrected for nitrogen.

ΔK_E = Change in the extracellular potassium content.

2. Potassium balance corrected for nitrogen,

$$bK' = bK - (3 \times bN'), \quad (2)$$

where:

bK = Potassium balance

3 = Factor relating potassium balance to nitrogen balance.

bN' = bN - (Δ NPN \times W)

where:

bN = Nitrogen balance.

Δ NPN = Change in serum non-protein nitrogen.

W = Total body water estimated as 60% of body weight.

3. Change in extracellular potassium content,

$$\Delta K_E = K_{E_2} - K_{E_1}, \quad (3)$$

where:

$$K_{E_1} = K_1 \times E_1$$

$$K_{E_2} = K_2 \times E_2$$

where:

K_1 = Initial potassium concentration in plasma.

K_2 = Final potassium concentration in plasma.

E_1 = Initial Volume of extracellular space calculated as 20% of body weight.

E_2 = Final Volume of extracellular space determined from changes in the chloride space.

RESULTS

The effect of extracellular pH change on the serum potassium concentration is illustrated (Figure 1) by the course of events in patient H. M. This patient had at the outset respiratory alkalosis associated with hepatic coma. Extracellular pH was altered by a combination of CO₂ inhalation and HCl infusion. No potassium was administered during the period of study and the cumulative potassium balance in excess of nitrogen at the end of four days was minus 63 mEq. The reciprocal relationship between extracellular pH and the serum potassium concentration is apparent. Also when the pH was normal the serum

potassium concentration was normal both before and after a loss of about 50 mEq. of potassium in excess of nitrogen. This observation is in agreement with the opinion that changes of less than 100 mEq. in potassium balance have a small effect *per se* on the serum potassium concentration (11).

The changes in serum electrolytes and electrolyte balances during the nine periods of study in five patients are presented in Table I and the important changes are summarized in Table II. In each instance a change in extracellular pH was associated with an inverse change in serum potassium concentration. Changes in intracellular potassium were small and in all but one instance opposite in direction to the change in serum potassium concentration. In the last column of Table II the change in serum potassium concentration per 0.1 unit change in extracellular pH has been calculated for each period of study. The range for four periods of correction of acidosis was 0.50 mEq. per L. to 1.20 mEq. per L. change per 0.1 pH change. The mean was 0.68 mEq. per L. change per 0.1 pH change. For correction of alkalosis the range was from 0.40 mEq. per L. to 1 mEq. per L. change pH 0.1 unit pH change. The

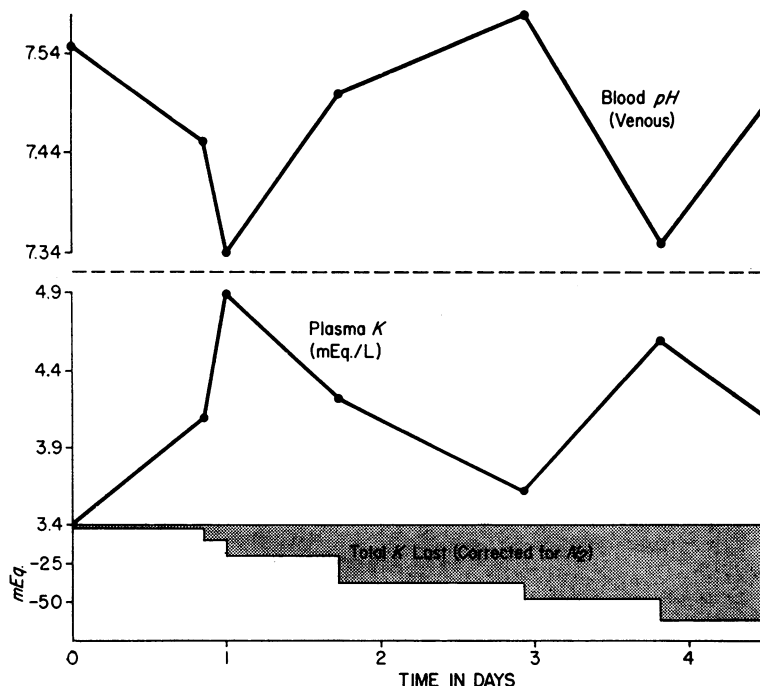


FIG. 1. SERIAL CHANGES IN BLOOD pH, PLASMA POTASSIUM CONCENTRATION AND POTASSIUM BALANCE IN PATIENT H. M.

TABLE I
Data of patients undergoing changes of extracellular pH*

Patient	Previous disorder	Body wt. Kg.	Dura- tion of exp.	Type of therapy	Intake			Output			Balance			Serum													
					Na	K	Cl	HCO ₃ ⁻	N	gm.	Na	K	Cl	N	gm.	bCl	bK	bN	gm.	bK [†]	NPN	mg. %	pH	K	Na	Cl	HCO ₃ ⁻
H. M.	Resp. alk.	68	18 hr.	CO ₂	0	0	0	0	0	0	44	12	42	4.3	-	42	-12	-4.3	-	4	Initial	23	7.55	3.4	142	116	19
																					Final	19	7.45	4.1	141	115	20
2.	Resp. alk.	—	18 hr.	HCl CO ₂	0	0	208	0	0	0	28.5	27	54	2.8	+154	-27	-2.8	-	6	Initial	19	7.44	4.1	141	115	20	
																					Final	29	7.34	5.1	137	118	13
3.	Metab. acid	—	14 hr.	—	0	0	0	0	0	—	28	43	5.5	-	43	-28	-5.5	-10	Initial	29	7.34	5.1	137	118	13		
																					Final	31	7.50	4.2	135	117	16.4
4.	Resp. alk.	—	32 hr.	—	0	0	0	0	0	5	22	39	1.4	-	39	-22	-1.4	-18	Initial	31	7.50	4.2	135	117	16.4		
																					Final	32	7.58	3.6	131	104	19.5
5.	Resp. alk.	—	17 hr.	HCl CO ₂	0	0	160	0	0	1.6	13	20	0.8	+140	-13	-0.8	-	6	Initial	32	7.58	3.6	131	104	19.5		
																					Final	36	7.35	4.6	126	104	14.9
J. R.	Metab. alk.	75	9.5 hr.	HCl NH ₄ Cl	0	0	360	0	2.5	29	21	52	2.6	+308	-21	-0.1	-	5	Initial	84	7.56	3.4	133	58	42.5		
																					Final	96	7.43	3.9	129	79	29.2
H. P.	Metab. acid	70	19 hr.	Sodium bicarb.	650	40	650	0	9	3	3	—	—	+37	+37	-1.5	+32.5	Initial	—	—	7.02	6.8	148	104	2		
																					Final	—	7.50	4.4	162	97	31
J. N.	Metab. acid	63	19 hr.	Sodium Lactate	300	0	0	0	0	0	0	0	0	0	0	0	0	0	Initial	103	7.20	9.3	132	106	11		
																					Final	103	7.35	7.4	143	96	33
J. D.	Metab. acid	45	17 hr.	Sodium bicarb.	500	0	0	500	0	74	31	66	3.6	-	66	-31	-3.6	-15	BUN	—	—	—	—	—	—	—	
																					Initial	125	7.02	6.4	139	119	5
																					Final	131	7.49	4.0	146	116	17.5

* All electrolyte balance data are expressed in mEq. All serum electrolyte concentrations are expressed in mEq. per L.
† bK[†] = Balance of potassium in excess of nitrogen.

TABLE II

Relationship between changes in extracellular pH and change in serum potassium concentration in nine experimental periods in five human subjects

Patient	Period	ΔK_s^*	ΔpH	ΔK_I^*	$\Delta K_s/0.1 \Delta pH$
H. M.	1	+0.7	-0.10	-13	0.63
	2	+1.0	-0.10	-25	1.00
	3	-0.9	+0.16	+3	0.56
	4	-0.6	+0.08	-16	0.75
	5	+1.0	-0.23	-25	0.45
J. R.	1	+0.5	-0.13	-12.5	0.40
H. P.	1	-2.4	+0.48	+60	0.50
J. N.	1	-1.9	+0.15	+14	1.27
J. D.	1	-2.4	+0.47	+8	0.51

* ΔK_s = Change in the serum potassium concentration in mEq. per L.

ΔK_I = Change in intracellular potassium in excess of nitrogen.

mean was 0.58 mEq. per L. change per 0.1 pH change. The mean for both groups was 0.63 mEq. per L. change in serum potassium concentration per 0.1 unit change in extracellular pH.

DISCUSSION

There are several problems inherent in attempts to quantitate the relationship between extracellular pH change and change in the serum potassium concentration. First, metabolic as compared with respiratory pH alterations may involve different intracellular buffering mechanisms and thus be quantitatively different. In these studies no effort was made to separate metabolic and respiratory disorders of extracellular pH. Second, changes in the serum potassium concentration induced by changes in total body potassium or changes in glycogen stores introduce additional variables. Difficulty in control of these variables may account for the wide range of pH induced change in the serum potassium concentration reported here.

In these studies changes in intracellular potassium in excess of nitrogen were in the opposite direction as the change in serum potassium concentration. Thus, the change in serum potassium concentration attributed to change in extracellular pH in most instances might be slightly greater than that recorded.

The results demonstrate consistently that acidosis increases and alkalosis decreases the serum potassium concentration independently of changes in total body potassium. As discussed elsewhere (7), the human muscle analyses of Mudge and

Vislocky (12) offer further support for the validity of this interrelationship.

Demonstration of this interrelationship between the serum potassium concentration and extracellular pH has several important clinical implications:

- 1) If the effect of pH is considered when interpreting the serum potassium concentration as an index of potassium need, this concentration becomes a more accurate guide to potassium therapy (11).
- 2) Extracellular pH must be controlled during experimental evaluation of other factors considered to influence the serum potassium concentration.
- 3) In the management of acute renal failure correction of acidosis and production of alkalosis will lower the serum potassium concentration and may facilitate prevention of potassium intoxication (cases H. P. and J. N.).

SUMMARY AND CONCLUSIONS

1. The effect of extracellular pH change on the relationship between the serum potassium concentration and intracellular potassium has been studied in 5 patients. A total of 9 experimental periods is described.

2. The results confirm the hypothesis that acidosis increases and alkalosis decreases the serum potassium concentration independently of changes in intracellular potassium. For every 0.1 unit change in extracellular pH there was an average inverse change of 0.6 mEq. per L. in the serum potassium concentration.

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