Influence of the GI Tract on Whole Body Acid-Base Balance

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INTRODUCTION

When $CaCl_2$ is given intravenously, it is neutral but ingested $CaCl_2$ causes metabolic acidosis. The different effect of the ingested $CaCl_2$ can be explained by the influence of the GI tract. The normal diet contains large quantities of alkali, acids, potential alkali, and potential acids, and the GI tract, through selective absorption of various constituents of acids and alkali in the diet, has substantial influences on the body's acid-base balance[1]. The GI tract is also the main route of non-renal loss of electrolytes, and such loss affects acid-base balance and alters urinary anion gap. The purpose of this talk is to discuss the mechanisms by which the GI tract regulates acid-base balance. The main part of the talk is on selective GI absorption of electrolytes and its effect on acid-base balance, but I will also briefly discuss the effect of selective GI loss of electrolytes and dietary changes on acid-base balance, with a particular emphasis on urinary anion gap, a topic which is attended with much misconception. In my discussion of these topics, I will include clinical examples and applications to illustrate the points.

INFLUENCE OF GI TRACT ON ACID-BASE BALANCE BY SELECTIVE ABSORPTION

The GI tract can influences acid-base balance, through selective reabsorption of various electrolytes. There are several rules that govern the GI absorption of ions. First, monovalent ions such as Na, K, Cl, and HCO_3, tend to be completely absorbed, whereas multivalent ions such as Ca, Mg, phosphate, and Al are not completely. Thus, for the monovalent ions, their food intake essentially equals their GI absorption. Second, GI absorption of multivalent ions depends not only on the nature of the substance but also on the interaction with other chemicals in food and drugs [3]. Third, soluble substances, e.g., Ca citrate, are better absorbed than insoluble substances, e.g., $CaCO_3$[4]. The solubility of a substance sometimes depends on HCl secretion and acid content of food. For example, insoluble $CaCO_3$ is converted to soluble $CaCl_2$ when it reacts with HCl in the stomach. Similarly, $CaCO_3$ is converted to Ca citrate when ingested with orange juice or to Ca acetate when ingested with vinegar.

The following section describes 5 different categories of chemical substances and the effects of their ingestion on acid-base balance.

1. Ingestion of non-absorbable or poorly absorbable cation accompanied by absorbable but non-metabolizable anion

As stated earlier, iv $CaCl_2$ is neutral, but ingested $CaCl_2$ is an acidifying agent. One might predict the effect of $CaCl_2$ on acid-base balance by looking at the differential absorption of the components of the ingested compound, namely Ca and Cl; virtually all of the Cl is absorbed but only a fraction of the Ca is absorbed[5]. The unabsorbed Ca reacts with CO_3 and is excreted

in stool; this represents loss of alkali. The actual reaction in the gut is as follows : $CaCl_2+2$ $NaHCO_3 \rightarrow 2NaCl+CaCO_3$. NaCl is absorbed and $CaCO_3$ is excreted in stool; the loss of alkali can be attributed to an exchange between Cl and CO_3. Absorbed $CaCl_2$ has a neutral effect on acid-base balance. When Cl exchanges with another non-metabolizable anion, HPO_4, there is no net gain or loss of alkali : $CaCl_2+Na_2HPO_4 \rightarrow 2NaCl+CaHPO_4$; NaCl is absorbed and $CaHPO_4$ is excreted in stool. The gain of acid after ingestion of $CaCl_2$ can be calculated as : chloride absorbed- (calcium absorbed+phosphate excreted in stool in exchange for chloride).

The effect of oral ingestion of $MgSO_4$ has not been studied carefully, and its effect on acid-base balance is difficult to predict. A likely substance to be formed in the gut following ingestion of Mg salts is a struvite, NH_4MgPO_4; struvite is slightly alkaline compared with $MgSO_4$, and its excretion in stool would represent excretion of alkali, and hence gain of acid to the body.

Unlike Ca which readily forms Ca carbonate, Mg does not form Mg carbonate, but can form $(MgCO_3)_4Mg(OH)_2$; the fecal excretion of this compound would also represent loss of alkali and hence gain of acid. In general Mg is better absorbed than Ca, and is a less effective binder of phosphate than Ca and therefore less is excreted as $MgHPO_4$[6]. Similarly, it can be predicted that $FeSO_4$ would result in gain of acid to the extent that SO_4 is absorbed in exchange for carbonate or an organic anion. Example : $FeSO_4+2NaHCO_3 \rightarrow FeCO_3+NaSO_4$; $NaSO_4$ is absorbed and $FeCO_3$ excreted in stool representing loss of alkali.

2. Ingestion of salts consisting of non-absorbable or poorly absorbable cation accompanied by absorbable and metabolizable anion

The amount of alkali gained when these salts are ingested depends on absorption of anions, which can can occur either with the accompanying cations, or in exchange for non-metabolizable anion such as phosphate[5]. Administration of $CaCO_3$ results in gain of alkali to the body when Ca is absorbed or when CO_3 is exchanged for HPO_4. Both processes require that $CaCO_3$ react with acid because $CaCO_3$ is nearly insoluble and will be mostly excreted in stool. HCl in the stomach or acids ingested with food such as citric acid in orange juice or acetic acid in vinegar can react with $CaCO_2$. The reaction in the stomach will be : $CaCO_3+2$ $HCl \rightarrow CaCl_2+H_2CO_3$. The fate of $CaCl_2$ thus formed will be the same as that of $CaCl_2$ ingested as such : Most of it, after reacting with $NaHCO_3$ in the duodenum, is converted back to $CaCO_3$ and is excreted in stool, some is absorbed as $CaCl_2$, and some is excreted as $CaHPO_4$ after reacting with Na- or K- phosphate.

Ingestion of organic salts of calcium such as calcium citrate, calcium lactate, calcium gluconate, and calcium acetate also results in gain of alkali. As with calcium carbonate, alkali gain occurs when these organic anions are absorbed either with calcium or in exchange for phosphate. Unlike calcium carbonate, however, organic salts of calcium do not need reactions with other acids for their absorption or binding of phosphate[6].

The overall alkalinizing effect of various calcium antacids depends less on the absorption of calcium than on the ability of calcium to bind phosphate, because the amount of calcium absorbed is usually much less than the amount excreted in stool in combination with phosphate. The phosphate-binding ability of these compounds depends in part on availability of soluble calcium. The amount of phosphate bound by calcium when calcium is ingested as $CaCl_2$ is comparable to that bound by aluminum ingested as $Al(OH)_3$. For each 100 meq of antacid ingested phosphate excreted was 11.9 meq with $CaCl_2$ and 11.4 meq with $Al(OH)_3$[5]. However, when Ca was ingested as the carbonate salt, only half as much

phosphate (6 meq) was removed for the same amount of calcium. One explanation is the poor solubility of $CaCO_3$. The solubility of $CaCO_2$ is enhanced by HCl, which will convert $CaCO_2$ to $CaCl_2$[7, 8]. On the other hand, excessive secretion of HCl could decrease the pH of the doudenum too low, resulting in conversion of HPO_4 to H_2PO_4; the latter is more readily absorbable than the the former, and thereby fecal excretion of phosphate could be reduced. In some patients with ESRD, the phosphate-lowering effect of $CaCO_3$ was enhanced by omeprazole[9]; a possible explanation is the prevention of the excessive reduction in pH of the duodenum by HCl. On the other hand, suppression of HCl secretion by treatment with a H2-blocker in patients with ESRD has shown to diminish the phosphate lowering effect of $CaCO_3$[10]. Yet, another study showed no significant difference with in phosphate binding capacity with the use of H2-blockers[11]. Calcium acetate is more effective binder of phosphate than calcium carbonate or calcium citrate, because it is more soluble than the others[6, 12]. Furthermore, citrate competes with phosphate for binding with calcium more effectively than acetate[6]. Consequently, GI absorption of Ca citrate is better than Ca acetate[4].

$Al(OH)_3$ or $Al_2(CO_3)_3$ had been widely used to treat hyperphosphatemia of chronic renal failure until the aluminum toxicity was recognized. Because aluminum is virtually unabsorbable, hydroxide or carbonate is absorbed only in exchange for phosphate. However, overall net gain of alkali is much greater with aluminum salts than calcium salts because Al is a more effective binder of phosphate than calcium.

The widely cited statement that $CaCO_2$ is an absorbable alkali whereas aluminum antacids are non-absorbable alkali is based on misinterpretation of the observation that milk-alkali syndrome occurs with ingestion of milk and $CaCO_3$ but not with the ingestion of milk and aluminum antacids[13]. However, the observation should not be considered as proof that more alkali was absorbed with Ca carbonate than with aluminum salts. Milk alkali syndrome results from increased alkali load and Ca absorption, and Ca carbonate contributes to the syndrome probably through increased Ca load. It should be noted that since those who developed milk-alkali syndrome were being treated for peptic ulcer diseases, their supernormal HCl secretion must have contributed to greater solubility of the ingested Ca carbonate and hence hyperabsorption of Ca. The binding of phosphate by $Al(OH)_3$ or Al carbonate is enhanced when it is administered in a colloidal form, because the non-colloidal forms does not have an enough contact area for chemical reactions[5, 6].

3. Ingestion of anion exchange resins

Anion exchange resins are made of non-absorbable and non-metabolizable poly-cations (usually quarternary ammonium groups attached to polystyrene skeleton) balanced by exchangeable anions[5]. They have either an alkalinizing or acidifying effect depending on whether the accompanying anion is metabolizable or non-metabolizable. When the counterion is non-metabolizable, e.g., Cl, its absorption in exchange for organic anions, carbonate, or bicarbonate represents loss of alkali. Cholestyramine, a chloride based anion exchange resin, has been used for treatment of hypercholesterelemia, and metabolic acidosis is a well known side effect. When Cl is exchanged for phosphate, there is no net gain or loss of alkali. When the counter-ion of the anion-exchange resin is metabolizable, e.g., acetate, a net gain of alkali occurs when the metabolizable anion is absorbed in exchange for chloride or phosphate. Exchange of acetate with other organic anions, carbonate, or bicarbonate is a neutral process for the acid-base balance.

4. Ingestion of cation exchange resins

The unabsorbable and non-metabolizable anion

in a cation exchange resin is usually sulfonate attached to polystyrene skeleton. The poly-anions of polystyrene skeleton are balanced by exchangeable and absorbable cations. In the case of sodium polystyrene sulfonate (Kayexlalate), the exchangeable cation is sodium. Although the specific purpose of administering sodium polystyrene sulfonate is to treat hyperkalemia by exchanging Na^+ for K^+, Na^+ exchanges with other cations including Ca^{++}, Mg^{++}, NH_4^+, and H^+. In fact, the resin has greater affinity for Ca and Mg than for Na^+ and K^+. Exchange of Na^+ for NH_4^+ or H^+ would result in gain of alkali to the body; exchange of Na^+ for K^+ is neutral. One might predict that exchange of Na^+ for Ca^{++} would have a neutral effect, but the net effect of such exchange usually results in gain of alkali for the following reasons. Normally, the bulk of Ca excreted in stool is in the form of insoluble calcium carbonate, which represents loss of alkali. When Ca^{++} in $CaCO_3$ is exchanged for Na^+ in Kayexalate, Na_2CO_3 is formed, which is converted to $NaHCO_3$ and then absorbed; calcium polystyrene sulfonate is excreted in stool. Administration of sodium polystyrene sulfonate has been shown to cause a substantial decrease in net acid excretion, up to 40 meq/day. This effect is more pronounced when the resin is administered with calcium salts or food that contains calcium[14, 15].

The urinary excretion of phosphate decreases when the resin is administered with calcium salts, probably because some Ca^{++} that would otherwise be excreted as insoluble calcium phosphate is exchanged for Na^+ in sodium polystyrene sulfonate, resulting in formation of soluble and readily absorbable sodium phosphate. The alkalinizing effect of $Al(OH)_3$ or Al carbonate is ordinarily limited to exchange of Al or CO_3 with phosphate in the diet, since Al is nearly unabsorbable. However, $Al(OH)_3$ or Al carbonate results in more gain of alkali when it is ingested with Na polystyrene sulfonate than when it is ingested with the usual diet because Al is exchanged for Na in Na polystyrene sulfonate, and the resulting NaOH or Na_2CO_3 (after its conversion to $NaHCO_3$) is readily absorbable[16, 17]. The reaction will be : Na polystyrene sulfonate + aluminum carbonate → $3Na_2CO_3$ + Al-polystyrene sulfonate. Similarly, the concomitant ingestion of $Mg(OH)_2$ and Na polystyrene sul fonate has an alkalinizing effect, because the exchange of Mg in $Mg(OH)_2$ with Na in Na-polystyrene sulfonate produces NaOH, which will be converted to $NaHCO_3$[18].

5. Calculation of net alkali content in a complex mixture of substances

Various chemical reactions described above cannot be predicted with accuracy, because many endogenous and exogenous factors are involved, such as the rate of HCl secretion and the nature of simultaneously ingested food or drugs. As stated earlier, the normally insoluble $CaCO_3$ in the absence of HCl secretion becomes soluble if it were administered with orange juice or ingested with vinegar. Neutral Na or K phosphate ingested without food is nearly completely absorbed. However, when it is ingested with calcium salts, a substantial amount of phosphate is lost in the stool as calcium phosphate.

The pattern of absorption of even a single chemical is difficult to predict. When ingested material is as complex as food which consists of literally thousands of different chemical substances, the prediction of the effect of food ingestion on acid-base balance by analyzing the absorption pattern of the component chemicals in food would be nearly impossible. Measurements are made instead by analyzing net alkali content of food and feces. The difference between these two is considered to be net alkali absorption. Net alkali content of food and feces is traditionally estimated by the electrolyte balance technique, i.e., the sum of non-combustible cations (Na+K+Ca+Mg) minus the sum of non-combustible anions (Cl+1.8 P).

The assumption in the use of this formula is that when non-metabolizable cations are accompanied by metabolizable anions, their subsequent absorption and metabolism of their anions would result in gain of alkali, and that ingestion of non-metabolizable anions accompanied by metabolizable cations would lead to a gain of acid[19, 20]. Hence, the difference between the two represents net gain of alkali. The concentrations of all of the electrolytes are expressed in meq, except phosphate, which is expressed in mmol and then multiplied by 1.8. The molar ratio of HPO_4/H_2PO_4 at pH 7.4 is 4/1, which gives an average valence of 1.8.

The actual pH of food or feces is not a determinant of the average valency of phosphate for the calculation of net alkali content, since that pH is relevant only in reference to the blood pH. The following examples will illustrate this point. Let us assume that a food contains 30 mmole of sodium phosphate and that the pH of the food is 7.4. Since the pK of H_2PO_4 is 6.8, 24 mmole will be in NaH_2PO_4, and 6 mmole in NaH_2PO_4 with a ratio of 4/1. Complete absorption of the mixture will not affect acid-base balance. The electrolyte balance technique also predicts a neutral effect on acid-base balance. The total content of non-combustible cation, i.e. Na, is 54 meq ($24\times2+6=54$) and the total content of non-combustible anion, i.e., phosphate, is also 54 meq (30 mmole multiplied by 1.8). Now add 9 meq of acetic acid to this mixture. Acetic acid will react with Na_2HPO_4 to form Na acetate and NaH_2PO_4. The mixture will contain 9 meq of Na acetate, 15 mmole of Na_2HPO_4, and 15 mmole of NaH_2PO_4. Since the ratio of HPO_4/H_2PO_4 is now 1, pH of the mixture will be 6.8. Upon absorption, 9 meq of Na acetate will generate 9 meq of alkali, while absorption of 15 mmole of Na_2HPO_4 and 15 mmole of NaH_2PO_4 into blood that has a pH of 7.4 will lead to consumption of 9 meq of alkali as 9 mmole of NaH_2PO_4 is converted to 9 mmole of Na_2HPO_4 in order to reestablish the ratio of HPO_4/H_2PO_4 at 4/1; net gain of acid is zero. Net alkali content of food after addition of acetic acid, calculated with the use of the electrolyte balance technique, is also zero since addition of acetic acid does not alter the total content of non-combustible cations and anions. Addition of 9 meq of HCl instead of acetic acid will result in the same overall changes in the ratio of HPO_4/H_2PO_4 as with the addition of acetic acid, but the net alkali content of the food mixture will be -9 meq. It will contain 9 meq of NaCl, and 15 mmole each of Na_2HPO_4 and NaH_2PO_4. Absorption of NaCl will have no effect on acid-base balance, but absorption of 15 mmole each of Na_2HPO_4 and NaH_2PO_4 into blood at pH 7.4 will lead to consumption of 9 meq of alkali, as 9 mmole of NaH_2PO_4 is converted to 9 mmole of Na_2HPO_4. Again, the answer is the same when the electrolyte balance technique is used. For the same reasons, the actual pH of stool is not important in estimating net alkali content of stool by the electrolyte balance technique.

For the calculation of net alkali content of food and feces, the only non-metabolizable ions assumed to be present are Na, K, Ca, and Mg, Cl and P. The reason for this assumption is simply that no other ions are present in normal food in any significant amount. Obviously other non-metabolizable cations such as lithium, iron, aluminum, counterions of anion or cation-exchange resins may be ingested in significant amounts, but these are ingested mainly as drugs. Other non-metabolizable anions that might be ingested include sulfate, nitrate, and bromide. However, normally they are ingested in minute quantities. Normal urine contains a substantial amount of sulfate, but sulfate that appears in the urine originates almost exclusively from sulphur-containing amino acids[21], and they are ingested as sulfate. Hence urinary excretion of sulfate is included as part of endogenous acid production. If sulfate is ingested as sulfate, it would lead to the overestimation of net G-I absorption of alkali by the electrolyte balance

technique. However, the measurement of urinary sulfate would lead to overestimation of endogenous acid production by exactly the same magnitude. Hence two errors will cancel out.

Some organic anions found in food are metabolized not at all or poorly by the human body. Tartarate, present in may fruits and used in baking powder, is such an anion. However, it has been shown that the bulk of the metabolism of ingested tartarate in humans is attributable to the actions of bacteria in the colon, and only about 14% of ingested tartarate appears in urine unchanged[22]. Some cations, e.g. choline, may be metabolized only by the colonic bacteria[23]. If organic anions or cations are metabolized by gut bacteria, their effects on acid-base balance would be the same as if they are metabolized in the body after absorption, and hence they could be treated as if they are metabolizable ions. Even if an organic anion in food is absorbed and excreted in urine unmetabolized, the estimation of overall acid-base balance would not be affected so long as net alkali absorption is measured by the electrolyte balance technique, and endogenous acid production by the excretion of urinary organic acid measured by the Van Slyke and Palmer method[24]. The presence of non-metabolizable organic anions in food would falsely increase the net G-I alkali absorption. On the other hand, the Van Slyke and Palmer method would falsely overestimate organic acid production by including non-metabolizable organic anions, by the same extent. The two errors would cancel each other out.

The measurement of G-I absorption of alkali by the analysis of food and feces is difficult and prone to inaccuracies. It assumes that the difference between dietary intake and fecal excretion represents GI absorption. However, some conditions must be met before we can accept such an assumption. First, the subjects must be adapted to their diet for a period sufficiently long to insure that the average fecal composition reflects the new fixed dietary conditions, and the time period of fecal collection should also be sufficiently long. Second, in order to assure complete evacuation of unabsorbed substances, there must be no intestinal disease. Furthermore, prolonged stool collection and accurate measurements of electrolytes in such inhomogeneous samples as stool and food require that study subjects be admitted to a clinical research center and kept on a special diet. For these reasons, no study has measured net GI absorption of alkali on a normal diet in an outpatient setting.

A technique based on the measurement of urinary electrolytes bypasses measurements of stool and food electrolytes, and offers the results that are equal or superior in accuracy[25]. In this technique, net G-I absorption of alkali is estimated as urinary non-combustible cations minus urinary non-combustible anions. The method is based on the assumption that absorbed non-combustible ions would all be ultimately excreted in the urine; the difference between amounts of non-combustible cations and non-combustible anions absorbed from the gut equals the difference between the amounts excreted in the urine under stable conditions. The validity of this assumption is supported by empirical as well as theoretical evidence.

Empirically, comparison of measurements of net G-I absorption of alkali by the urinary method with those by the food and fecal electrolyte method showed highly significant correlation ($r=0.99$; $p<0.0001$). The theoretical evidence is as follows. Since the total extracellular content of divalent ions is small (about 45 meq of Ca, 30 meq of Mg, and 30 meq of P), in the absence of substantial net flux from or into bone or cell, the amounts of these ions excreted in the urine must be very close to the amounts absorbed from the G-I tract. Net flux of calcium, magnesium, and phosphate into or out of bone in a normal adult

without active bone formation or bone resorption is negligible. Even a substantial net formation or resorption of bone would have a trivial effect on net G-I absorption of alkali estimated by the urinary electrolyte technique. For example, net loss of 100 mg of Ca per day by dissolving hydroxyapapatite would cause a gain of mere 2.3 meq of alkali to the extracellular fluid[26].

In a steady state, amounts of Na, K, and Cl excreted in the urine should be nearly equal to amounts absorbed from the G-I tract. Urinary Na and Cl content in a given 24 hour period may be different from amounts absorbed during the same period, because extracellular volume tends to fluctuate. However, daily fluctuations in Na and Cl excretion would not affect the calculation of net G-I absorption of alkali, since these ions tend to be retained or lost together. For the same reasons, extrarenal loss of salt, e.g. in sweating, would have little effect on the calculation of net alkali absorption from the G-I tract. To the extent that some Na or K is lost with HCO_3 or lactate in sweat, alkali will be lost, but such loss is negligible

Even if urinary excretion of non-combustible ions did not precisely quantify the pattern of the G-I absorption in individual cases, a mean value of net GI absorption of alkali in a large population would be accurate, even in an outpatient setting. Thus, it is now possible to measure the net G-I absorption of alkali in a large population ingesting their usual diet in an outpatient setting. Such measurement has been made, and the amount of alkali absorbed was found to be substantial, 29.6 meq/day (unpublished observation).

The overriding importance of food and GI tract on urinary anion gap.

Urine anion gap is measured as the sum of urine Na and K minus urine Cl, and the usual normal value is given as about 40 meq/day[27]. It should be noted that in contrast to serum anion gap, the unit of measurement of urinary anion gap is best expressed as meq/day. Because urine volume varies greatly, values given in concentrations are not as useful, although values expressed in meq/L have been used[28]. The main usefulnees of urinary anion gap is thought to be an indirect measure of urine ammonia concentration. Specifically, it has been suggested that decreased urinary anion gap denotes increased urine ammonia excretion, and increased urinary anion gap indicates reduced urine ammonia excretion suggestive of various types of renal tubular acidosis. Several studies have argued for[28-31] and against[32-34] utility of urinary anion gap in the differential diagnosis of hyperchloremic metabolic acidosis. Some showed good correlation with urine ammonia and some showed poor correlation with urine ammonia. Most of these studies wrongly emphasized the importance of other unmeasured cations and anions in the urine as determinants of urinary anion gap, neglecting the importance of dietary contribution to the urine anion gap. The following discussion is intended to rectify this misunderstanding.

The most important principle in the understanding of urinary anion gap is that since GI absorption of Na, K, and Cl are nearly complete, the urinary excretion is primarily determined by dietary intake of these ions. There are two exceptions to this rule. One is non-renal loss of these electrolytes, mainly GI losses. For example, vomiting causes selective loss of Cl accompanied by little Na and K, and therefore urine will contain relative excess of Na and K over Cl; the result is increased urinary anion gap. The reverse occurs in diarrhea. Diarrheal fluid contains more Na and K than Cl; hence urine would contain relative excess of Cl over Na and K; the result is decreased urinary anion gap.

The other exception to the rule is a acute change in body's acid-base status. With acute acid-base disorders, a temporary discrepancy occurs between dietary intake and urinary excretion of these ions. For example in acute respiratory alkalosis,

the kidney excretes bicarbonate accompanied by Na and K, resulting in increased urinary anion gap. In acute respiratory acidosis, the reverse would occur; increased ammonia excretion accompanied by Cl, resulting in decreased urinary anion gap. In the development phase of diabetic ketoacidosis, urinary excretion of ketone anions accompanied by Na and K should result in increased urinary anion gap, whereas during the recovery phase of diabetic ketoacidosis increased urinary excretion of ammonium accompanied by Cl would result in the reverse.

In chronic states, no change in urinary anion gap is expected unless disease states somehow alter the pattern of dietary intake. There has been attempt to utilize urinary anion gap in differential diagnosis of various metabolic acidoses. If there was any correlation found, the findings must have been purely accidental. For example, if a patient with chronic RTA eats the same diet as a normal person, the pattern of intake of Na, K, and Cl and urinary anion gap must be about the same as a normal person, no matter what urinary ammonia excretion might be. Patients with incomplete type I RTA often has alkaline urine pH with increased urine ammonia, whereas patients with type IV RTA tends to have acidic urine pH with reduced urine ammonia. However, if both patients were eating the same food, urinary anion gap must be about the same.

Similarly, if a patient with chronic renal insufficiency were ingesting regular diet, there is no reason to expect urinary anion gap to be different from normal persons. Ingestion of phosphate binders such as aluminum or calcium salts could affect acid-base balance and change urine ammonia excretion, but would not alter urinary anion gap, as long as the diet remains unchanged. On the other hand, the patient alters the dietary intake in response to disease states, urinary anion gap would change. For example, if a patient with chronic renal insufficiency decides to reduce meat intake as a means of reducing phosphate intake, urinary anion gap is likely to decrease, since meat contains a large amount of K and phosphate, but little Cl. On the other hand, if a patient eats more citrate fruits, which is rich in K but no Cl, urinary anion gap would tend to increase, whereas an increased ingestion of wheat and barley, which contains more Cl than Na, is likely to reduce urinary anion gap.

NH_4Cl administration has been used to demonstrate that increased urinary ammonia reduces urinary anion gap, and the finding is often cited as evidence of a close inverse correlation between urine ammonia and urinary anion gap. However, urinary anion gap in this instance increases not because urine ammonia increased but because Cl is given without Na or K. Administration of sulfuric acid would increase urine ammonia to the same extent as that of HCl, but will not increase urinary anion gap. Conversely, if Cl is given with either choline or lithium (as long as it is not accompanied by Na or K), the same increase in urinary anion gap would occur, but without a concomittant increase in urinary ammonium excretion. The key determinant of urinary anion gap is the composition of ingested electrolytes.

In summary, chronic changes in urinary anion gap is dictated by diet, not by the metabolic states or renal function. Two exceptions are selective GI loss and acute acid-base disorders. This is not to say that urinary anion gap has no clinical utility. The most useful function of urinary anion gap is to determine the severity of diarrhea. If a patient has diarrhea and metabolic acidosis, the physician might be interested knowing whether diarrhea was materially important in causing metabolic acidosis. It is often difficult to quantitate the magnitude of diarrhea, and the measurement of urinary anion gap can provide an semiquantitative answer.

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