DISEASE OF THE MONTH

Metabolic Alkalosis

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In this article, we review metabolic alkalosis, one of the most common fluid and electrolyte disorders. An understanding of the diagnosis and treatment of entities that cause metabolic alkalosis requires a knowledge of the processes responsible for this disorder.

Generation and Maintenance of Metabolic Alkalosis

The pathogenesis of metabolic alkalosis involves both the generation and maintenance of this disorder (1). The generation of metabolic alkalosis refers to the addition of new HCO_3^- to the blood as a result of either loss of acid or gain of alkali. New HCO_3^- may be generated by either renal or extrarenal mechanisms. Because the kidneys have an enormous capacity to excrete HCO_3^-, even vigorous HCO_3^- generation may not be sufficient to produce sustained metabolic alkalosis. To maintain a metabolic alkalosis, the capacity of the kidney to correct the alkalosis must be impaired, or, equivalently, the capacity to reclaim HCO_3^- must be enhanced. On the other hand, increased capacity for HCO_3^- reclamation in the absence of generation is also insufficient to cause metabolic alkalosis. Thus, the two ingredients required for the pathogenesis of metabolic alkalosis are the generation of new HCO_3^- combined with an augmentation in the capacity of the kidney to reclaim the filtered HCO_3^-.

Renal Generation of Metabolic Alkalosis

Bicarbonate may be generated from renal or extrarenal sources (Table 1). In most cases, the renal generation of HCO_3^- involves three features that function synergistically to increase H^+ secretion in the distal nephron and cause renal net acid excretion to exceed metabolic acid production: (*1*) high distal delivery of Na^+ salts; (*2*) mineralocorticoid excess; and (*3*) K^+ deficiency. In general, metabolic alkalosis, which is generated by renal mechanisms, is maintained by similar processes in the distal nephron. In addition, enhanced HCO_3^- reclamation in more proximal portions of the nephron may contribute to maintenance by allowing longer segments of the distal tubule to be exposed to a bicarbonate-free urine. Instead of expending its comparatively limited H^+ secretory capacity on HCO_3^-

reabsorption, H^+ secreted by the distal nephron can titrate NH_4^+ and phosphate and thus increase renal net acid excretion.

A simple increase in distal delivery of Na^+ salts without sustained or increased mineralocorticoid activity, as occurs in volume expansion, does not increase net acid excretion. Similarly, increased mineralocorticoid activity in the absence of distal Na^+ delivery, as occurs in volume contraction, fails to increase net acid excretion. To augment net acid excretion and thus generate a metabolic alkalosis through renal mechanisms, delivery of Na^+ salts to the distal nephron must occur with sustained or increased mineralocorticoid activity. Aldosterone directly stimulates electrogenic Na^+ reabsorption in the cortical collecting duct by stimulating both apical membrane Na^+ permeability and the Na^+/K^+-ATPase. This leads to an increased negative voltage of the tubule lumen that secondarily increases the rates of K^+ and H^+ secretion. For every H^+ secreted into the lumen, a HCO_3^- is returned to the blood. In the absence of distal Na^+ delivery, aldosterone cannot stimulate Na^+ reabsorption and cannot alter the voltage, resulting in no change in secretion of H^+ and K^+ (2). Although aldosterone has been shown to have a direct stimulatory effect on H^+ secretion in the distal nephron, the observation that mineralocorticoids do not stimulate renal K^+ or H^+ excretion in subjects on a low-salt diet suggests that this direct effect is quantitatively of lesser importance than the indirect voltage effect.

Relatively high distal Na^+ delivery and high mineralocorticoid levels are seen in patients with primary increases in distal Na^+ delivery and in patients with primary increases in mineralocorticoid levels. The word "primary" here refers to the fact that the changes are not occurring secondary to changes in volume. Thus, a primary increase in distal Na^+ delivery occurs with diuretics that work proximal to the cortical collecting duct, such as osmotic diuretics, carbonic anhydrase inhibitors, loop diuretics, and thiazides. These result in increased distal Na^+ delivery and increased Na^+ excretion. The latter leads to volume contraction, which increases mineralocorticoid levels. The result is increased distal Na^+ delivery and increased mineralocorticoid levels. Bartter's syndrome and Mg^{2+} deficiency are in many respects similar to diuretic ingestion in that distal delivery of Na^+ is high in these disorders as a result of impaired reabsorption of NaCl in the loop of Henle.

Similarly, a primary increase in mineralocorticoid levels, as occurs with an aldosterone-secreting adenoma, directly increases distal Na^+ reabsorption, resulting in volume expansion, which suppresses proximal Na^+ reabsorption and increases distal Na^+ delivery. The result again is increased distal Na^+ delivery and increased mineralocorticoid levels. In both

Table 1. Generation of metabolic alkalosis

Extrarenal
- excessive loss of acid
  - loss of acid into gastric juice: vomiting, nasogastric suction
  - intestinal acid loss: villous adenoma, congenital chloridorrhea
  - translocation of acid into cells: sodium deficiency
- excessive gain of bicarbonate
  - oral or parenteral intake of bicarbonate
  - metabolism of lactate, ketones, or other organic anions to bicarbonate

Renal
- coupling of high mineralocorticoid activity and high distal sodium delivery
- persistent mineralocorticoid excess
- potassium deficiency

cases, there is also increased K^+ excretion, which results in K^+ depletion, which further enhances distal H^+ secretion and net acid excretion. The mechanisms responsible for this are discussed below.

Posthypercapnic alkalosis is also generated in the kidney. Posthypercapnic alkalosis refers to patients who are hypercapnic and develop a compensatory metabolic alkalosis due to renal HCO_3^- retention. After the P_{CO_2} is corrected, the high blood [HCO_3^-] now represents a primary metabolic alkalosis, which may be maintained by the kidney (see below).

Extrarenal Generation of Metabolic Alkalosis

Extrarenal factors may also be responsible for the generation of metabolic alkalosis. Acid loss, as in vomiting or nasogastric suction, leads to addition of new HCO_3^- to the blood. Alkali gain, as in the milk-alkali syndrome or with the use of injectable $NaHCO_3$ during cardiopulmonary resuscitation, may also generate metabolic alkalosis. Acid may also be translocated within the body, producing acidosis in one compartment and alkalosis in the other. This may occur with severe potassium deficiency. Finally, relative bicarbonate generation (increased concentration) may be induced by extracellular volume contraction. In all of these circumstances, for metabolic alkalosis to be sustained, the capacity of the kidney to reclaim bicarbonate must also be enhanced.

Maintenance of Metabolic Alkalosis

Reduced effective arterial blood volume is the mechanism responsible for the maintenance of metabolic alkalosis in the majority of patients. In general, this form of alkalosis has been referred to as hypochloremic metabolic alkalosis. However, careful studies have demonstrated that the key to maintenance of metabolic alkalosis is not the Cl^- concentration, but rather the total body Cl^- (3). The key role played by total body Cl^- is understandable by considering the different types of anions that may contribute to extracellular fluid volume. Organic

anions such as citrate and lactate are rapidly metabolized to HCO_3^- and thus will not contribute to extracellular fluid volume. Nonreabsorbable anions such as sulfate and phosphate are rapidly excreted by the kidney, and again will not contribute to extracellular fluid volume. The only remaining anions are Cl^- and HCO_3^-. Thus, if one is trying to correct a metabolic alkalosis maintained by volume contraction, the only anion that may be added to the extracellular fluid that will be retained and not converted to HCO_3^- is Cl^-.

The mechanisms by which volume contraction maintains metabolic alkalosis have been recently reviewed and will only be summarized briefly (4). In some settings, volume contraction is associated with a decrease in GFR, which would decrease the filtered load of HCO_3^-, decreasing the quantity of HCO_3^- that must be reabsorbed to maintain metabolic alkalosis. In addition, volume contraction increases the capacity of the proximal tubule to reabsorb HCO_3^- by two mechanisms. First, volume contraction leads to a decreased permeability of the paracellular pathway to HCO_3^- and thus inhibits the back-leak of HCO_3^- from the blood into the tubule lumen. Second, decreases in extracellular fluid volume lead to changes in circulating and local levels of hormones, which stimulate proximal tubule transcellular H^+ secretion, such as angiotensin II, norepinephrine, and dopamine. Finally, volume contraction decreases Cl^- delivery to the cortical collecting tubule. Because HCO_3^- secretion in the collecting tubule requires luminal Cl^- to exchange for HCO_3^-, the rate of HCO_3^- secretion will be decreased.

K^+ depletion affects renal function in many ways that can affect the kidney's ability to maintain metabolic alkalosis. K^+ depletion causes a decrease in GFR, which would lower the filtered load of HCO_3^- and secondarily contribute to maintenance of metabolic alkalosis. In addition, K^+ depletion has been demonstrated to stimulate rates of proximal and distal tubule H^+ secretion (5–7). Finally, K^+ depletion leads to adaptive increases in the enzymes that synthesize NH_4^+, causing increased rates of ammoniagenesis in the proximal tubule (8). Although all of these effects contribute to the generation and maintenance of metabolic alkalosis, K^+ deficiency also inhibits aldosterone secretion, an effect that inhibits acidification. The net result is that K^+ deficiency alone has only a small variable effect on overall acid base balance (9,10). In humans, K^+ deficiency alone does not cause significant metabolic alkalosis unless associated with volume contraction. However, a few patients have been described in whom severe K^+ depletion (serum [K^+] < 2 mEq/L) is the sole factor responsible for generation and maintenance of metabolic alkalosis (11).

By contrast, if K^+ depletion occurs in a setting in which mineralocorticoid secretion is nonsuppressible, then the stimulatory effects on renal acidification dominate, and metabolic alkalosis will develop. Thus, in the setting of primary mineralocorticoid excess in which extracellular fluid volume is expanded, K^+ deficiency significantly enhances the generation and maintenance of metabolic alkalosis. Indeed, in patients with primary hyperaldosteronism, patients with the most severe K^+ depletion have the most marked metabolic alkalosis

(12,13). Correction of the K^+ deficit will return the plasma HCO_3^- concentration toward normal in this setting.

Mineralocorticoids contribute to the maintenance of metabolic alkalosis by stimulating H^+ secretion in the distal nephron (14). As discussed earlier, mineralocorticoids are important in the generation and maintenance of metabolic alkalosis only when high levels are associated with increased distal delivery of Na^+. This will occur with primary increases in mineralocorticoids in which mineralocorticoid-induced volume expansion ensures high distal delivery of Na^+. Diuretics that act proximal to the cortical collecting duct, Bartter's syndrome, and Mg^{2+} deficiency may also cause this scenario, with volume contraction leading to high aldosterone levels and the defect in more proximal Na^+ absorption maintaining distal Na^+ delivery. In patients with extrarenal generation of alkalosis, filtered loads of HCO_3^- may exceed the capacity of the proximal tubule leading to distal delivery of Na^+ and HCO_3^- and thus allow high mineralocorticoid levels to play a role by increasing H^+ secretion and decreasing the magnitude of bicarbonaturia.

Clinical Syndromes Associated with Metabolic Alkalosis

Metabolic alkalosis will be seen in clinical conditions that lead to the generation and maintenance of alkalosis (Table 2). From a clinical point of view, it is useful to divide these conditions into two groups based on whether they are associated with volume contraction or volume expansion.

Volume Contraction

These conditions are those in which the clinical disorder leads to generation of metabolic alkalosis and a contracted effective arterial volume. The alkalosis may be generated renally or extrarenally. These conditions are characterized by contraction of the effective arterial volume, a circumstance usually associated with reduced distal delivery of Na^+ salts and a volume-mediated stimulation of the renin-angiotensin-aldosterone system. Ordinarily, this would not be associated with renal generation of alkalosis. However, if distal Na^+ delivery is inappropriately increased, as with use of diuretics, Bartter's syndrome, and Mg^{2+} deficiency, or secondary to the presence of a poorly reabsorbable anion, then net acid excretion will be stimulated and alkalosis may result. Thus, in these conditions the renal defect leads to generation of the alkalosis and volume contraction, which secondarily causes the kidney to maintain the alkalosis.

Posthypercapnic metabolic alkalosis refers to a condition in which chronic hypercapnia leads to a compensatory metabolic alkalosis. During this period of hypercapnia, renal retention of HCO_3^- is associated with a chloruresis. This likely occurs because $NaHCO_3$ retention causes volume expansion, which causes the kidney to excrete $NaCl$. The net result is that patients with hypercapnia have increased total body $NaHCO_3$ and decreased total body $NaCl$. When hypercapnia is corrected, the kidney will attempt to correct the alkalosis by excreting HCO_3^-. However, if $NaCl$ is not provided, bicarbonaturia will

Table 2. Syndromes of metabolic alkalosis

Effective volume contraction, secondary increase in aldosterone, BP normal or low
- gastrointestinal, dietary, or other nonrenal generation
  vomiting or nasogastric suction
  chloride wasting diarrhea
  villous adenoma
  contraction alkalosis
- renal generation
  diuretics (mercurial, loop, or thiazide diuretics)
  volume depletion with increased distal delivery of poorly reabsorbable anions
  Bartter's syndrome
  magnesium deficiency
  posthypercapnic state

Extracellular fluid volume expansion with mineralocorticoid effect, increased BP
- increased renin, increased aldosterone
  renal artery stenosis
  accelerated hypertension
  renin secreting tumor
- decreased renin, increased aldosterone
  primary aldosteronism
  adrenal adenoma
  bilateral adrenal hyperplasia
  dexamethasone-responsive adrenal hyperplasia
  carcinoma
- decreased renin, decreased aldosterone
  Cushing's syndrome
  exogenous mineralocorticoid
  congenital adrenal enzyme defect
  11β hydroxylase deficiency or inhibitor
  Liddle's syndrome

Renal insufficiency
- exogenous bicarbonate load in setting of decreased GFR
- milk-alkali syndrome

Miscellaneous
- potassium deficiency

lead to volume contraction, which will halt the bicarbonaturia and lead to maintenance of the metabolic alkalosis. When $NaCl$ is provided, the kidney corrects the alkalosis.

A number of extrarenal conditions lead to the generation of metabolic alkalosis associated with volume contraction, which secondarily causes the kidney to maintain the alkalosis. These conditions include vomiting, nasogastric suction, villous adenoma, congenital chloridorrhea, and severe volume contraction.

In all of these conditions, alkalosis leads to renal K^+ wasting, and the resultant K^+ depletion contributes to the maintenance of metabolic alkalosis. However, volume contraction remains the major factor responsible for maintenance. If one corrects the K^+ deficit without correcting the volume deficit, metabolic alkalosis remains, whereas correction of the volume

deficit with persistent hypokalemia leads to correction of the metabolic alkalosis (15,16).

Volume Expansion with Mineralocorticoid Excess

These conditions are associated with a primary increase in mineralocorticoid activity. Increased mineralocorticoid activity is considered primary in that it persists in the face of expansion of the effective extracellular fluid volume, which normally would lead to its suppression. As long as dietary Na^+ is normal, distal delivery of Na^+ salts will be plentiful, and urinary K^+ and net acid excretion will be increased. This will result in K^+ deficiency and the generation and maintenance of metabolic alkalosis. As discussed earlier, the resulting hypokalemia further increases net acid excretion in the presence of nonsuppressible mineralocorticoid activity.

From the clinical point of view, conditions with primary increases in mineralocorticoid activity are most easily divided into three groups based on circulating levels of renin and aldosterone. First, patients may have increased levels of renin, which cause increased levels of aldosterone. Increased renin production may result from conditions such as renal artery stenosis, accelerated hypertension, or a renin-secreting tumor. Hypersecretion of aldosterone also may be primary, in which case it will be associated with suppressed renin levels. Conditions that may give rise to primary hyperaldosteronism include adrenal adenomas, bilateral adrenal hyperplasia, dexamethasone-responsive adrenal hyperplasia, and adrenal carcinoma. Dexamethasone-responsive adrenal hyperplasia has been shown to be due to a translocation, which causes the promoter of the 11β hydroxylase gene, an ACTH responsive gene, to move to the 18 hydroxylase gene, a rate-limiting gene in aldosterone synthesis (17). The net result is that ACTH causes increased expression of aldosterone synthase, increasing aldosterone synthesis, and secretion. Provision of glucocorticoids to the patients suppresses ACTH, thus inhibiting aldosterone synthesis.

A third group of patients displays evidence of excessive mineralocorticoid activity attributable to a mineralocorticoid agent other than aldosterone. Measured levels of renin and aldosterone are low. Examples of these syndromes include adrenogenital syndromes in which there is oversecretion of nonaldosterone mineralocorticoids such as deoxycorticosterone, and the various causes of Cushing's syndrome, in which secretion of hydrocortisone is increased. Whether patients with Cushing's syndrome develop hypokalemic alkalosis likely depends on their relative levels of cortisol and 11β hydroxylase. The enzyme 11β hydroxylase is expressed in mineralocorticoid-responsive cells and is responsible for inactivating cortisol in these cells (18). This reaction, which converts the active cortisol to the inactive cortisone, is responsible for the limited mineralocorticoid activity of cortisol. When cortisol levels exceed the capacity of 11β hydroxylase to inactivate it, it binds to the mineralocorticoid receptor and elicits mineralocorticoid effects. In addition to its relevance to Cushing's syndrome, decreases in the activity of 11β hydroxylase may result in hypermineralocorticoid states. Such decreases in activity may

be genetic or may be due to ingestion of an inhibitor, glycyrrhizic acid, which is present in licorice and chewing tobacco.

An additional genetic disorder that appears as a hypermineralocorticoid state with low renin and aldosterone levels is Liddle's syndrome. This condition differs from the conditions above in that hypertension and hypokalemic alkalosis are not responsive to mineralocorticoid receptor antagonists. Thus, the defect is actually downstream of the mineralocorticoid receptor. Studies have now demonstrated that Liddle's syndrome is due to a mutation in the luminal membrane Na^+ channel of the cortical collecting duct, which increases its activity (19). This leads to enhanced Na^+ reabsorption and voltage changes similar to those associated with hypermineralocorticoid states, resulting in hypertension, hypokalemia, and alkalosis.

Renal Insufficiency

In the setting of significant renal disease, HCO_3^- clearance is decreased, and severe metabolic alkalosis may occur after exogenous HCO_3^- administration. Similarly, renal insufficiency is a critical event in the pathogenesis of milk-alkali syndrome. In this syndrome, consumption of large quantities of milk and calcium-containing antacids results in hypercalcemia and metabolic alkalosis.

Approach to the Patient with Metabolic Alkalosis

The approach to the patient suspected of metabolic alkalosis begins with analysis of the arterial blood gas, ensuring that one is dealing with a primary metabolic alkalosis rather than a compensation for a respiratory acidosis (Figure 1). After documenting that the patient has a metabolic alkalosis, further evaluation is based on consideration of the factors responsible for maintenance. As shown in Table 2, the causes of metabolic alkalosis may be conveniently divided between those in which alkalosis is maintained by a decreased effective arterial volume, those in which it is maintained by the combination of high aldosterone and high distal Na^+ delivery, and those in which it is maintained by renal failure. In general, it is obvious when patients have renal failure, and these entities will not be discussed further.

The first key step in the approach, therefore, is the assessment of the effective arterial volume. As in most patients, effective arterial volume may be assessed by the physical examination, emphasizing the presence or absence of postural changes in pulse and BP. The serum uric acid and the blood urea nitrogen:creatinine ratio are also helpful. Finally, urinary electrolytes are helpful. Patients with a low effective arterial volume should have low urinary Na^+ and Cl^- concentrations. In these patients, bicarbonaturia or excretion of other nonreabsorbable anions may lead to inappropriately high urinary Na^+ concentrations even in the presence of volume contraction. Thus, the urinary Cl^- is frequently more useful in these patients.

When urinary Cl^- is low, this usually points to a contracted effective arterial volume. If this is associated with a high urine Na^+, the patient likely is excreting a nonreabsorbable anion or

Approach To The Patient With Metabolic Alkalosis

$\downarrow$

Check Arterial Blood Gas To Exclude Compensation
For Respiratory Acidosis

$\downarrow$

Assess Volume Status

$\downarrow$ EABV

Normal or $\uparrow$ EABV

Conditions associated with $\uparrow$
mineralocorticoid effect

$\downarrow$

Measure renin and aldosterone

$\downarrow$ Urine [Cl]

$\uparrow$ Urine [Cl]
1. Active diuretic use
2. Mg++ deficiency
3. Bartter's syndrome

$\downarrow$ Urine [Na]
1. Posthypercapneic
2. Remote use of diuretics
3. Vomiting (not active)

$\uparrow$ Urine [Na]
1. Vomiting (active)
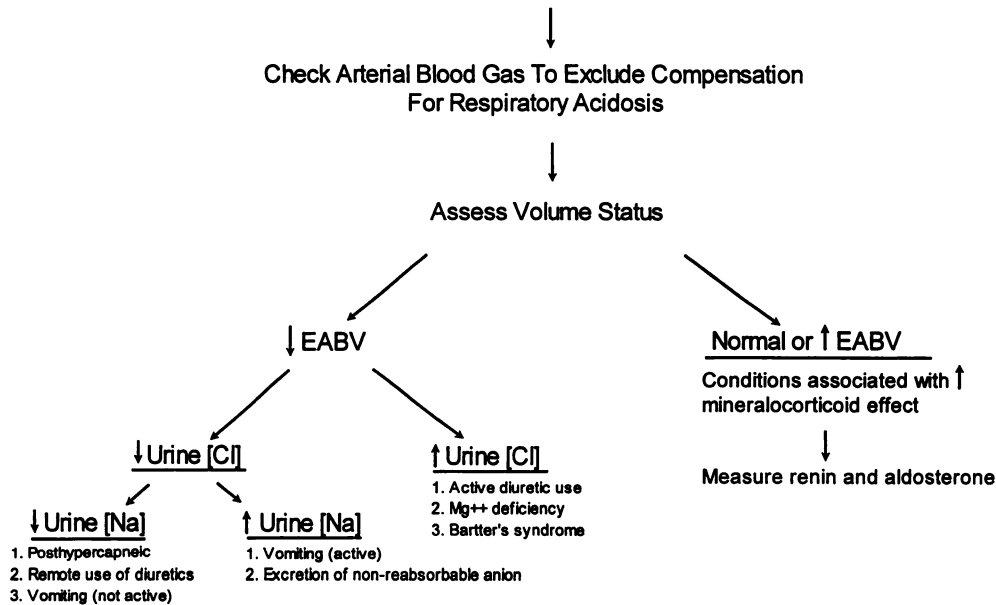2. Excretion of non-reabsorbable anion

Figure 1. Approach to the patient with metabolic alkalosis. EABV, effective arterial blood volume.

bicarbonate. These may be distinguished using the urine pH. A urine pH of 7 or 8 indicates significant bicarbonaturia. A urine pH of less than 6.5 suggests that another nonreabsorbable anion is responsible, such as ketoanions or an antibiotic. Once the question of a nonreabsorbable anion is raised, the specific one responsible is usually clear. If a patient has significant bicarbonaturia, it suggests that the patient has generated a metabolic alkalosis of greater magnitude than the kidney is being driven to maintain. Because the kidney cannot generate and correct an alkalosis at the same time, this suggests extrarenal generation. Whether this is due to vomiting, nasogastric suction, or a Cl^- wasting, diarrhea is usually obvious.

A high urinary Cl^- in a patient with volume contraction suggests diuretics, Bartter's syndrome, or Mg^{2+} depletion. If urine Na^+ and Cl^- are low, the cause of the alkalosis may be posthypercapnic, diuretics (without a diuretic effect at the time of measurement), or vomiting (likely not actively vomiting).

If the patient has hypertension and appears euvolemic/volume expanded, one is likely dealing with a primary increase in mineralocorticoids. Workup of these patients is extremely important because these disorders represent a common cause of treatable hypertension. Here the measurement of renin and aldosterone represents the next step. If measured renin and aldosterone are both elevated, it is important to be certain that the patient was not volume-contracted at the time of measurement. This can frequently be accomplished by a saline suppression test. This is not a problem if renin levels are suppressed. Table 2 lists the various disease entities that should be considered based on the results of the renin and aldosterone measurements.

One difficult scenario is a patient with hypertension who is taking a thiazide diuretic. In this case, it is not clear whether the

hypokalemic alkalosis is due to a primary increase in mineralocorticoids or whether it is merely due to the thiazide. Here the serum Na^+ can be very helpful. In general, patients on thiazides all tend to have low serum Na^+ concentrations, whereas patients with mineralocorticoid excess syndromes tend to have high serum Na^+ concentrations. The presence of a $[Na^+]$ of 144 to 146 mEq/L in a patient on thiazides suggests a primary increase in mineralocorticoids.

Clinical Consequences of Metabolic Alkalosis

Metabolic alkalosis is generally considered a benign condition by most physicians. However, there is evidence that suggests that under certain circumstances metabolic alkalosis may contribute significantly to mortality. In fact, a direct relationship has been shown between increasing blood pH and hospital mortality in patients with a pH of greater than 7.48 (20,21). The demonstration that high arterial blood pH correlates with mortality does not establish a cause/effect relationship. It is certainly plausible that conditions associated with high mortality cause metabolic and respiratory alkalosis, making alkalosis merely a marker of a poor prognosis. However, there are a number of reasons to believe that high blood pH may contribute to the poor prognosis. This is based on some of the known pathophysiologic effects of a high blood pH.

First, increases in blood pH (alkalemia) cause respiratory depression. This effect of metabolic pH changes on respiration is mediated via both central and peripheral chemoreceptors. Although the effects of metabolic alkalosis on respiration are well appreciated, the effects of alkalosis to decrease tissue oxygen delivery are less well appreciated. Alkalosis can decrease oxygen delivery by two possible mechanisms. First, by the Bohr effect, alkalosis leads to a shift in the oxygen dissociation curve of hemoglobin, which decreases the ability of

hemoglobin to release oxygen in peripheral tissues. Thus, even in the absence of changes in blood flow, alkalosis may lead to marked decreases in oxygen delivery to tissues.

In addition to the Bohr effect, alkalosis is a potent vasoconstrictor. Numerous studies have shown that increases in pH associated with decreases in Pco_2 (respiratory alkalosis) lead to vasoconstriction and decreased perfusion of the brain, heart, and peripheral circulation. Respiratory alkalosis is used clinically to decrease cerebral blood flow in patients with cerebral edema. Although it is unclear from studies in man and whole animals whether pH changes due to metabolic alkalosis have the same effect, in vitro studies show that pH is the critical determinant of vascular smooth muscle tone, regardless of whether pH is altered by changes in Pco_2 or HCO_3^- concentration (22,23). Studies in humans and intact animals are complicated by expansion of the circulating blood volume with a $NaHCO_3$ infusion and by other possible secondary effects such as rapid renal potassium wasting in acute metabolic alkalosis. It seems most likely that blood pH is a determinant of vascular resistance such that organ perfusion may be compromised in metabolic, as well as respiratory, alkalosis. This may be a more severe problem in patients with chronic metabolic alkalosis, which is frequently associated with contraction of the circulating blood volume (see below).

Alkalosis-induced vasoconstriction, together with the Bohr effect, may cause clinical tissue hypoxia in certain settings. For example, hyperventilation has been shown to precipitate chest pain, ST segment elevation, and spasm on coronary angiography in patients with Prinzmetal's angina (24). Similarly, hyperventilation has been shown to cause angina in the presence or absence of coronary artery disease (25,26). Alkalosis has also been reported to induce cardiac arrhythmias, which are unresponsive to antiarrhythmics and respond only to correction of the alkalosis. Unfortunately, this is only substantiated by a number of case reports, and it is difficult to prove an increased incidence.

In summary, evidence suggests that alkalemia can decrease oxygen delivery to tissues, and this may become a key factor in certain critically ill patients. Alkalemia constricts vascular smooth muscle in vitro and appears to decrease tissue perfusion in vivo. This, along with inhibition of oxygen release from hemoglobin, leads to decreased tissue oxygen delivery, which is demonstrable clinically with regard to the heart where coronary artery spasm, angina, arrhythmias, and congestive heart failure may be precipitated. Most likely, oxygen delivery to the brain is also compromised in ill patients with alkalosis, but it is frequently clinically difficult to distinguish brain hypoxia from other causes of encephalopathy. As will be referred to later, critically ill patients, in whom perfusion of the heart and brain is essential, should likely have their alkalosis aggressively corrected.

Treatment of Metabolic Alkalosis

The treatment of metabolic alkalosis is best achieved by correcting the factor responsible for maintenance. In addition, it is frequently helpful to correct the factor that generated the alkalosis. If patients have a metabolic alkalosis that is main-

tained by volume contraction, administration of NaCl should correct the alkalosis. Although it is not necessary to give K^+ to these patients to correct the alkalosis, one frequently administers KCl to correct the hypokalemia. Other treatment approaches that may be used are Mg^{2+} replacement in Mg^{2+} deficiency, K^+ replacement in severe K^+ deficiency, removal of the source of excess mineralocorticoid in appropriate patients, cessation of diuretic therapy, or cessation of nasogastric suction. In patients in whom nasogastric suction is necessary, addition of H_2 receptor blockade may decrease the tendency to generate the metabolic alkalosis.

In certain patients, it may be difficult to correct the factors responsible for maintenance of metabolic alkalosis. This occurs most frequently in patients whose metabolic alkalosis is maintained by decreased effective arterial volume but whose cardiovascular system cannot tolerate administration of NaCl. In these situations, one must ask how important it is to correct the metabolic alkalosis. On the basis of the above discussion, patients in whom one would want to aggressively correct metabolic alkalosis would include: (1) patients with chronic lung disease in whom intubation is imminent or extubation is difficult and in whom metabolic alkalosis needs to be corrected to improve the drive to respiration; (2) patients with myocardial ischemia with evolving myocardial infarction, patients who are having chest pain postinfarction, or patients with unstable angina; and (3) ill patients with cerebral dysfunction in whom cerebral hypoperfusion is a possible contributing factor.

If metabolic alkalosis needs to be treated aggressively and cannot be treated by correcting the cause of the generation or maintenance, a number of options remain. First, ammonium chloride may be given (27). This is generally a safe way to administer acid if given orally. However, if given intravenously, especially in patients with liver disease, ammonium chloride may cause ammonia toxicity. Arginine hydrochloride has been used in the past to lower the plasma $[HCO_3^-]$ but has since been taken off the market because of life-threatening hyperkalemia.

The most commonly used approach to correct alkalosis in these difficult patients is administration of carbonic anhydrase inhibitors such as acetazolamide. Carbonic anhydrase catalyzes the dehydration of luminal carbonic acid (produced when filtered HCO_3^- reacts with secreted H^+) to water and CO_2 and the hydration of cellular CO_2 to carbonic acid, allowing the formation of H^+ for secretion into the luminal fluid. The uncatalyzed dehydration of carbonic acid occurs very slowly. By inhibiting the activity of this enzyme, carbonic anhydrase inhibitors inhibit renal acidification and thus cause the kidney to at least partially correct the metabolic alkalosis (28). The magnitude of the bicarbonaturia induced is directly related to the serum HCO_3^- concentration. As the HCO_3^- concentration falls, the clinical effectiveness of the drug declines in a parallel manner. As a result, only rarely does the plasma HCO_3^- concentration return to normal.

Acetazolamide is frequently used in patients with chronic respiratory acidosis who develop a metabolic alkalosis. Normally, in patients with chronic respiratory acidosis the capacity

of the kidney to reabsorb bicarbonate increases, resulting in an increase in plasma HCO_3^- concentration. Use of loop diuretics in such patients, as in the treatment of cor pulmonale, may result in further increases in the serum HCO_3^- concentration. In this setting, the induction of a metabolic alkalosis can depress ventilation, aggravating both the hypoxemia and hypercapnia. Normally, the metabolic alkalosis can be treated by discontinuing the diuretic and administering NaCl. In the patient who is significantly edematous, however, this approach may not be practical. In this circumstance, acetazolamide can be used to inhibit HCO_3^- reabsorption and thus lower serum HCO_3^- concentration.

A potential problem that is associated with use of carbonic anhydrase inhibitors in patients with lung disease is a worsening of hypercapnia. Carbonic anhydrase is normally present within red blood cells and is involved in CO_2 movement into red cells in peripheral tissues and movement from red cells into the alveoli in the lungs. Thus, carbonic anhydrase inhibition can prevent red cell uptake of CO_2 in peripheral tissues and can prevent CO_2 release in the lung. The latter may lead to an increase in the P_{CO_2} of the arterial blood, whereas the former may lead to an additional increase in P_{CO_2} in peripheral tissues. Generally, patients with normal lungs respond to this by increasing respiration and preventing the increase in the P_{CO_2} of the arterial blood. However, patients with lung disease cannot respond adequately, and further increases in arterial P_{CO_2}, as well as even greater increases in unmeasured tissue P_{CO_2}, may be dangerous to the patient.

A safe approach to the aggressive treatment of metabolic alkalosis that has gained support is the use of hydrochloric acid infusions (29,30). In general, hydrochloric acid may be safely administered as a 0.15 to 0.25 Normal solution in normal saline or D5W given through a central line. It is imperative that the position of the central line in the superior vena cava be verified by chest x-ray before initiating infusion. There are a large number of reports published showing that such an infusion is safe (29,30). If the physician wishes, the HCl may be added to an amino acid solution in total parenteral nutrition and given centrally (31). In addition, there is also a report in which HCl was given in an amino acid solution with intralipid through a peripheral vein (32).

The preferred treatment of metabolic alkalosis in patients with volume expansion and primary mineralocorticoid excess is to remove the underlying cause of the persistent mineralocorticoid activity. When this is not possible, therapy is directed at blocking the actions of the mineralocorticoid at the level of the kidney. The potassium-sparing diuretics are effective agents in blocking the actions of mineralocorticoids in the kidney and are commonly used in the treatment of these disorders. Mineralocorticoid receptor blockers such as spironolactone are effective in these patients, with the exception of Liddle's syndrome, in which the defect is distal to the receptor. Spironolactone inhibits Na^+ reabsorption by blocking the binding of aldosterone to its cytoplasmic receptor, thereby inhibiting aldosterone-induced Na^+ reabsorption. The decrease in luminal electronegativity impairs distal acidification as a result of the decrease in the electrical driving force for H^+

secretion into the tubule lumen. Spironolactone can further limit distal H^+ secretion because this drug not only inhibits aldosterone-stimulated Na^+ reabsorption, but also blocks the direct stimulatory effect of aldosterone on the H^+ secretory pump.

Na^+ channel blockers such as amiloride and triamterene are also effective in these patients. These drugs directly inhibit the luminal membrane Na^+ channel, decreasing the luminal electronegativity of the collecting duct and secondarily impairing renal K^+ and H^+ losses. The net effect is inhibition of renal Na^+ retention, K^+ loss, and increases in renal net acid excretion, resulting in prevention of hypertension and hypokalemic alkalosis.

As discussed earlier, Liddle's syndrome is characterized by hypokalemic metabolic alkalosis and volume expansion, but is not due to mineralocorticoid excess. Rather, this disorder results from overactivity of the Na^+ channel in the distal nephron. Predictably, use of spironolactone to block the mineralocorticoid receptor is without effect in this disorder. By contrast, the electrolyte abnormalities and hypertension are normalized by use of the sodium channel blockers triamterene and amiloride.

Summary

In summary, the kidney possesses numerous mechanisms that help to prevent metabolic alkalosis. Maintenance of metabolic alkalosis for any length of time means that renal homeostatic mechanisms for HCO_3^- excretion have been disrupted. Understanding the mechanisms that may perturb the kidney's ability to correct alkalosis will lead to improved clinical approaches to differential diagnosis and treatment of the patient. Although metabolic alkalosis is frequently not dangerous, in certain settings metabolic alkalosis may contribute to mortality and should be treated aggressively.

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