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Metabolic Alkalosis

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Metabolic alkalosis is common—half of all acid-base disorders as described in one study (1). This observation should not be surprising since vomiting, the use of chloruretic diuretics, and nasogastric suction are common among hospitalized patients. The mortality associated with severe metabolic alkalosis is substantial; a mortality rate of 45% in patients with an arterial blood pH of 7.55 and 80% when the pH was greater than 7.65 has been reported (2). Although this relationship is not necessarily causal, severe alkalosis should be viewed with concern, and correction by the appropriate intervention should be undertaken with dispatch when the arterial blood pH exceeds 7.55.

Metabolic alkalosis occurs when a primary pathophysiologic process leads to the net accumulation of base within or the net loss of acid from the extracellular fluid (ECF); typically, the intracellular compartment becomes more acidic in potassium-depletion alkalosis (3). Unopposed by other primary acid-base disorders, metabolic alkalosis is recognized by increases in both arterial blood pH—alkalemia—and plasma bicarbonate concentration. The increase in arterial blood pH promptly, normally, and predictably depresses ventilation resulting in increased $PaCO_2$ and the buffering of the alkalemia. The $PaCO_2$ increases about 0.5 to 0.7 mmHg for every 1.0 mM increase in plasma HCO_3 concentration (4). Although a $PaCO_2$ greater than 55 mmHg is uncommon, compensatory increases to 60 mmHg have been documented in severe metabolic alkalosis. Failure of an appropriate compensatory increase in $PaCO_2$ should be interpreted as a mixed acid-base disturbance in which a stimulus to hyperventilation—primary respiratory alkalosis—accompanies primary metabolic alkalosis.

Classification and Definitions

Metabolic alkalosis has been classified by the primary organ system involved, the response to therapy, or the underlying pathophysiology; the latter is presented in Table 1. The most common group—those due to chloride depletion—can, by definition, be corrected without potassium repletion. The other major grouping is that due to potassium depletion, usually with mineralocorticoid excess. Metabolic alkalosis due to both potassium and chloride depletion also may occur and is not rare.

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Bicarbonate or base loading, whether exogenous or endogenous (as in bone dissolution), is rarely a sole cause of significant persistent metabolic alkalosis because the normal kidney is so efficient at excreting bicarbonate. Such transient states may occur during and immediately after an oral or intravenous infusion of $NaHCO_3$ or base equivalent, *e.g.*, citrate in transfused blood or fresh frozen plasma (5). They may also occur after the successful treatment of ketoacidosis or lactic acidosis, as these organic anions are metabolized to bicarbonate. Finally, after successful correction of hypercapnia in respiratory acidosis before the kidney can excrete the bicarbonate retained for compensation, metabolic alkalosis may occur transiently provided that chloride intake is adequate. In these transient states, the urinary pH should be relatively alkaline ($>$6.2).

The course of metabolic alkalosis can be divided into generation, maintenance, and correction phases (6). Generation occurs by loss of protons from the ECF into the external environment or into the cells, or by gain of base by the oral or intravenous route or from the base stored in bone apatite. Disequilibrium occurs in the generation phase when the resultant elevation of plasma bicarbonate exceeds the capacity of the renal tubule to reabsorb bicarbonate. Transient bicarbonaturia (urinary pH $>$6.2) with resulting sodium loss ensues until a new steady state of chronic metabolic alkalosis is achieved and bicarbonate excretion ceases. At this point, the urine is relatively acidic—so-called paradoxical aciduria—and metabolic alkalosis is likely to be in the maintenance phase.

Pathophysiology of Chloride-Depletion Alkaloses

Generation

Chloride may be lost from the gut, kidney, or skin. The loss of gastric fluid, which contains 60 to 140 mM HCl and lesser variable concentrations of sodium and potassium (7), results in alkalosis because bicarbonate generated during the production of gastric acid returns to the circulation. In the Zollinger-Ellison syndrome or pyloric stenosis, these losses may be massive. Although sodium and potassium loss in the gastric fluid varies in concentration, the obligate urinary loss of these cations is intensified by bicarbonaturia, which occurs during disequilibrium. Gastrocystoplasty, recently introduced for bladder augmentation, may also result in urinary HCl losses sufficient to produce alkalosis (8).

Villous adenomas of the colon usually produce a hyperchloremic metabolic acidosis because of the loss of large volumes of colonic fluid, rich in potassium and bicarbonate. However, 10 to 20% of these tumors will secrete chloride rather than

Table 1. Etiologies of metabolic alkalosis

Chloride depletion
gastric losses: vomiting, mechanical drainage, bulimia
chloruretic diuretics: bumetanide, chlorothiazide, metolazone, etc.
diarrheal states: villous adenoma, congenital chloridorrhea
posthypercapneic state
dietary chloride deprivation with base loading: chloride-deficient infant formulas
gastrocystoplasty
cystic fibrosis (high sweat chloride)
Potassium depletion/mineralocorticoid excess
primary aldosteronism: adenoma, idiopathic, hyperplasia, renin-responsive, glucocorticoid-suppressible, carcinoma
apparent mineralocorticoid excess
primary deoxycorticosterone excess: 11β- and 17α-hydroxylase deficiencies
drugs: licorice (glycyrrhizic acid) as a confection or flavoring, carbenoxolone
Liddle syndrome
secondary aldosteronism
adrenal corticosteroid excess: primary, secondary, exogenous
severe hypertension: malignant, accelerated, renovascular
hemangiopericytoma, nephroblastoma, renal cell carcinoma
Bartter and Gitelman syndromes and their variants
laxative abuse, clay ingestion
Hypercalcemic states
hypercalcemia of malignancy
acute or chronic milk-alkali syndrome
Other
carbenicillin, ampicillin, penicillin
bicarbonate ingestion: massive or with renal insufficiency
recovery from starvation
hypoalbuminemia

bicarbonate with potassium, and thus result in metabolic alkalosis (9).

Congenital chloridorrhea, an autosomal recessive disease, is caused by defective apical chloride/bicarbonate exchange in the colon and perhaps the ileum because of a mutation of the Down-Regulated in Adenoma (DRA) gene (10). This defect results in copious diarrhea with major chloride losses (11). Gastric and jejunal functions are normal. Although fecal sodium and potassium concentrations are normal, the unremitting watery stool results also in sodium, potassium, and volume losses. The renal response mediated by aldosterone is intense sodium and water reabsorption at the expense of proton and potassium secretion, thereby further promoting alkalosis.

Chloruretic agents such as chlorothiazide, furosemide, and their congeners all directly produce the loss of chloride, sodium, and fluid in the urine (12). These losses, in turn, promote metabolic alkalosis by several possible mechanisms. (*1*) Diuretic-induced increases in sodium delivery to the distal nephron accelerate potassium and proton secretion (13). (*2*) ECF volume contraction stimulates renin and aldosterone secretion, which blunts sodium loss but accelerates the secretion of potassium and protons. (*3*) Potassium depletion will independently augment bicarbonate reabsorption in the proximal tubule (14) and (*4*) stimulate ammonia production, which, in turn, will increase urinary net acid excretion. Urinary losses of chloride exceed those for sodium and are associated with alkalosis even when potassium depletion is prevented (15).

Respiratory acidosis is compensated by accelerated renal bicarbonate reabsorption in various nephron segments and increased urinary chloride excretion (16,17). The patient with chronic respiratory acidosis is chloride-depleted, and the kidney will maintain this deficit until the hypercapnia is corrected. When respiratory acidosis is corrected, accelerated bicarbonate reabsorption, which is no longer appropriate, persists if sufficient chloride is not available and "post-hypercapneic" metabolic alkalosis remains.

Skin losses of chloride may generate alkalosis in cystic fibrosis. Alkalosis may even be the presenting feature in adolescence with a few of the several hundred mutations in the cystic fibrosis transmembrane regulator (CFTR) gene (18).

Maintenance

The cessation of events that generate alkalosis is not necessarily accompanied by resolution of the alkalosis. To account for maintained metabolic alkalosis in these instances, the kidney must retain bicarbonate by either a decrease in GFR with an accompanying decrease in filtered bicarbonate, or by an increase in bicarbonate reabsorption, or by both mechanisms. Because chloride-depletion alkaloses are usually characterized by concurrent deficits of sodium, potassium, and fluid, as well as chloride, controversy has arisen regarding which of these deficits is responsible for the maintenance of the alkalosis.

Kassirer and Schwartz showed that experimental chloride-depletion alkalosis effected by gastric suction could be completely corrected by chloride repletion with either KCl or NaCl, thus eliminating deficits of sodium or potassium *per se* as specific causes of maintenance in these circumstances (19). Based on this and other studies, they concluded that chloride repletion was pivotal in the correction (20), but a role for volume repletion *per se* was not excluded. Subsequently, Cohen provided evidence of a primary role for volume expansion (21).

A widely accepted hypothesis for the pathophysiology of the maintenance and correction of chloride-depletion alkalosis based on volume proposed the following (6): Volume contraction accompanying alkalosis augments fluid reabsorption in the proximal tubule, and, because bicarbonate is preferentially reabsorbed compared with chloride in this segment, alkalosis is maintained. With ECF volume expansion, fluid reabsorption in the proximal tubule is depressed, delivering more bicarbonate and chloride to the distal nephron, which possesses a substantial capacity to reabsorb chloride but a limited one for bicarbonate. As a result, chloride is retained, bicarbonate excreted, and alkalosis corrected. In this construct, chloride administra-

tion has only a permissive role for volume expansion, which itself is regarded as the extrarenal impetus for correction.

This "classical" hypothesis based on volume has been reappraised in a series of studies of both acute and chronic chloride-depletion alkalosis in human and rat (22). In these studies, chloride-depletion alkalosis has been completely corrected by the administration of any of several non-sodium chloride salts despite persistently low GFR, decreased plasma volume, negative sodium balance, decreasing body weight, continuing urinary potassium loss, persistently high plasma aldosterone concentration, and continued bicarbonate loading—all of which would, if anything, maintain or generate alkalosis. During either expansion or contraction of ECF volume, alkalosis was not corrected without chloride replacement (23). Even during sustained volume contraction, chloride promptly induced bicarbonaturia and progressively corrected the alkalosis. In humans with diuretic-induced alkalosis maintained for 5 d by chloride restriction, alkalosis was corrected as chloride was repleted quantitatively despite decreased GFR, renal blood flow, and the decreased plasma volume that persisted throughout the correction (15). In contrast, men given equal amounts of neutral sodium phosphate became volume-expanded with worsening of their alkalosis. Thus, we would extend the earlier conclusion of Schwartz and coworkers to state that chloride is necessary and sufficient for the correction of chloride-depletion alkalosis (20). Volume depletion is a commonly associated but not a causative or essential factor for the maintenance of alkalosis.

We have proposed that intrarenal mechanisms responsive to chloride depletion can plausibly account for the maintenance of alkalosis regardless of the status of the ECF volume. In the absence of volume depletion, chloride depletion appears to decrease GFR by tubuloglomerular feedback (24) by an alteration in the signal perceived by the macula densa—tubule fluid chloride concentration or osmolality. Such a protective response by the kidney would blunt fluid and sodium losses, which are likely to attend the bicarbonaturia frequently encountered during disequilibrium alkalosis. Chloride depletion also increases renin secretion by a macula densa mechanism, resulting in increased aldosterone secretion that may be disproportionate to the magnitude of an accompanying hypokalemia and thereby augment potassium wasting.

Although normal functioning of the proximal tubule is essential to permit appropriate bicarbonate reabsorption, the collecting duct appears to be the major nephron site for altered electrolyte and proton transport in both maintenance of and recovery from metabolic alkalosis. The collecting duct is heterogeneous anatomically and functionally throughout its length with regard to both cells and segments, but the major cell stimulated by chloride-depletion alkalosis is the type B intercalated cell in the cortical segment (25,26). During maintenance, bicarbonate secretion does not occur because insufficient chloride is available for bicarbonate exchange and bicarbonate reabsorption is maintained distally in the medullary segments. When chloride is administered and luminal or cellular chloride concentration or amount increases, bicarbonate is promptly excreted and alkalosis is corrected. When a defect in renal transport itself is the proximate cause of alkalosis, *i.e.*, Bartter syndrome, other alterations in renal electrolyte transport likely occur.

Pathophysiology: Potassium Depletion/ Mineralocorticoid Excess Alkalosis

Generation

Dietary potassium depletion is associated with modest metabolic alkalosis and with an increase in intracellular sodium and proton concentrations and suppression of aldosterone (27,28). Metabolic alkalosis is generated primarily by an intracellular shift of protons. However, potassium depletion is also associated with enhanced renal ammonia production, and a contribution of increased net acid excretion has not been excluded in humans (29,30). Similarly, administration of aldosterone causes only a slight degree of metabolic alkalosis if potassium depletion is prevented (31). While escape from the sodium-retaining effect of mineralocorticoids occurs at the expense of persistent intravascular and ECF volume expansion and resulting hypertension, escape does not occur from their potassium-wasting effect. When potassium depletion and mineralocorticoid excess occur together, prominent metabolic alkalosis is common.

Mineralocorticoid excess either primary or secondary can occur for a myriad of causes (Table 1). Acting at its receptor in the principal cell of the collecting duct, mineralocorticoid stimulates the apical sodium channel and basolateral Na,K-ATPase, and increased sodium reabsorption promotes potassium secretion through the apical potassium channel. Associated sodium retention usually leads to hypertension, as in primary aldosteronism, or often to edema, as in secondary aldosteronism, *e.g.*, in cardiac failure.

Low plasma renin and high circulating aldosterone characterize the primary disorders, whereas high plasma renin and aldosterone characterize the secondary causes. Most all of the primary disorders are due to adrenal neoplasia or hyperplasia except the glucocorticoid-suppressible variety. This autosomal dominant disease is caused by a chimeric gene formed by the overlap of the gene for 11 β-hydroxylase with that for aldosterone synthase (32). The former is regulated by adrenocorticotropin hormone (ACTH), whereas the latter normally is not. As a consequence of this chimera, aldosterone secretion becomes responsive to ACTH and aldosterone excess results.

Apparent mineralocorticoid excess syndromes have more complex pathophysiologies and are associated with low circulating aldosterone and low plasma renin. Several of these involve genetic alterations in the enzymatic pathway for adrenosteroid biosynthesis; others are drug-induced (33). Licorice, found in confections, chewing tobacco, some soft drinks, and herbal preparations, and carbenoxolone, a drug used for the treatment of peptic ulcer, contain glycyrrhetinic acid or its derivative, either of which potently inhibit the renal isoform of 11 β-hydroxysteroid dehydrogenase present only in the principal cell. This enzyme normally shunts cortisol, which exceeds the concentration of aldosterone by a ratio of 100:1, to the inactive cortisone. Thus, with these inhibitors, cortisol acts

at the promiscuous mineralocorticoid receptor. In contrast, Liddle syndrome, an autosomal dominant disorder with variable clinical expression, is characterized by a structural defect in a subunit of the apical sodium channel in the principal cell of the collecting duct that leads to unregulated sodium reabsorption with the cascade of events as above (34).

Several consequences of potassium depletion likely contribute to the renal maintenance of metabolic alkalosis. Potassium secretion is stimulated by enhanced luminal sodium delivery, increased aldosterone concentrations, increased cellular potassium activity, or diminished availability of luminal chloride. Proximal tubule bicarbonate reabsorption is enhanced and may be secondary to intracellular acidosis, which facilitates proton secretion. In the cortical collecting tubule, aldosterone stimulates proton secretion and bicarbonate reabsorption either directly or indirectly by an increased lumen-negative potential (35). Type A intercalated cells in the outer medullary segment increase in size and number in potassium depletion and maybe engaged in potassium conservation at the expense of continued bicarbonate reabsorption probably through both H-ATPase and H,K-ATPase. The important role of intracellular acidosis in potassium-depletion alkalosis is supported by correction of the alkalosis by infusion of potassium without any suppression of renal net acid excretion (36); correction is assumed to occur by the movement of potassium into and of protons out of the cell, which titrates ECF bicarbonate.

Some disorders may be characterized by both chloride and potassium depletion, which serve to intensify the alkalosis. They are usually associated with sodium losses and normotension or hypotension. Downregulation of chloride transporters occurs in potassium depletion (37), and thus severe potassium depletion, in particular, is accompanied by renal chloride wasting.

Alkalosis in Bartter (BS) and Gitelman (GS) syndromes and their variants are likely dependent on both potassium and chloride depletion. Most patients with BS are usually detected in infancy with failure to thrive. A primary hereditary defect in coupled Na,K,2Cl reabsorption in the thick ascending limb of Henle's loop explains renal sodium, potassium, and chloride wasting, macula densa and volume depletion-stimulated activation of the renin-aldosterone system, and high renal production of prostaglandin E_2 (38). Both prostaglandin E_2 excess and severe potassium depletion can further impair Na,K,2Cl reabsorption in the ascending limb. Hypercalciuria is prominent while serum magnesium concentration is usually normal. Hypokalemia is less severe in "variant" BS likely because the mutation is in the luminal ROMK channel, which facilitates potassium recycling from the thick ascending limb of Henle's loop into the lumen—a step essential for the normal functioning of the Na,K,2Cl cotransporter.

In contrast, GS often presents in adults, is less severe, is often heterozygotic, and, at least in the United States, is more common than BS. The genetic defect in this syndrome is in the thiazide-sensitive NaCl cotransporter in the distal convoluted tubule (38). It is associated with hypocalciuria and hypomagnesemia but not increased urinary prostaglandins.

Gut potassium losses such as in laxative abuse or geophagia are rarely associated with severe alkalosis. Urinary potassium is low in laxative abuse, and plasma bicarbonate is rarely above 30 to 34 mEq/L (39).

Pathophysiology: Miscellaneous

Milk-alkali syndrome in which both bicarbonate and calcium are ingested produces alkalosis by several mechanisms, including vomiting, hypercalcemia (which increases bicarbonate reabsorption), and a reduced GFR. Cationic antibiotics in high doses can cause alkalosis by obligating bicarbonate to the urine. Hypoalbuminemia causes mild metabolic alkalosis because of the diminution of the negative charge that albumin normally contributes to the anion gap and the shift in the buffering curve for plasma.

Clinical and Diagnostic Aspects

The symptoms of metabolic alkalosis *per se* are difficult to separate from those of chloride, volume, or potassium depletion. Apathy, confusion, cardiac arrhythmias, and neuromuscular irritability (related in part, perhaps, to a low ionized plasma calcium) are common when alkalosis is severe (40). Compensatory hypoventilation may cause hypoxia or contribute to pulmonary infection in very ill or immunocompromised patients.

The cause of chronic metabolic alkalosis is often evident on the initial assessment of the patient with a careful history and physical examination (Table 1). In the absence of blood gas measurements, an increase in the anion gap—due primarily to lactate—and hypokalemia favor the diagnosis of metabolic alkalosis over respiratory acidosis when plasma chloride is low and bicarbonate high.

Urinary chloride and potassium measurements before therapy are useful diagnostically. Low urinary chloride ($<$10 mEq/L) characterizes alkalosis in which chloride depletion predominates unless a chloruretic diuretic is present; it remains low until chloride repletion is nearly complete. A urinary potassium concentration of $>$30 mEq/L in the presence of hypokalemia establishes renal potassium wasting, which is indicative of an intrinsic renal defect, diuretics, or high circulating aldosterone. Conversely, a urinary potassium concentration of $<$20 mEq/L suggests extrarenal potassium loss. When metabolic alkalosis due primarily to potassium depletion is suggested, the presence of a severe alkalosis should prompt a search for additional causative factors, such as chloride depletion or base ingestion. If the cause of the alkalosis is not readily apparent, the urine should be screened for diuretics.

Surreptitious induction of alkalosis as with diuretics or vomiting (bulimia) can be difficult to detect, but certain clues may help to establish the diagnosis: The patients are more often female; an underlying psychiatric abnormality may be present; the severity of alkalosis may fluctuate; the patient can easily obtain diuretics; intermittently alkaline urine can occur with acute-on-chronic vomiting; patients with surreptitious vomiting may have blackened teeth enamel and scarred knuckles. Diuretic abuse usually leads to more severe potassium depletion than vomiting.

Correction

Treatment is directed in two general areas: (*1*) correction of existing deficits and (*2*) prevention of continuing losses. With regard to the latter, drugs, agents, or other interventions that generate alkalosis should be discontinued whenever possible.

Chloride-Responsive Alkaloses

Although replacement of the chloride deficit is essential, selection of the accompanying cation—sodium, potassium, or proton—is dependent on assessment of ECF volume status, the presence and degree of associated potassium depletion, and the degree and reversibility of any depression of GFR. If kidney function is normal, bicarbonate and base equivalents will be excreted with sodium or potassium and metabolic alkalosis will be rapidly corrected as chloride is made available.

If depletion of chloride and ECF volume coexist, as is most common, isotonic NaCl is the appropriate therapy and simultaneously corrects both deficits. In patients with overt signs of volume contraction, the administration of a minimum of 3 to 5 L of 150 mEq/L NaCl is usually necessary to correct volume deficits and metabolic alkalosis. When the ECF volume is assessed as normal, total body chloride deficit can be estimated by the formula: 0.2 × Body weight (kg) × Desired increment in plasma chloride (mEq/L). The replacement of continuing losses of fluid and electrolytes must be added to this regimen. As the chloride deficit is corrected, a brisk alkaline diuresis will occur with a decrease in plasma bicarbonate toward normal.

Plasma potassium concentration should be followed serially. Concomitant potassium repletion is clinically indicated to avoid other potentially harmful effects of potassium depletion. Potassium can be provided conveniently by adding KCl 10 to 20 mEq/L to the regimen.

In the clinical setting of volume overload such as in congestive heart failure, administration of NaCl is clearly inadvisable. Chloride should be repleted with KCl as above unless hyperkalemia is present or if the ability to excrete a potassium load is a concern.

Intravenous HCl is indicated if NaCl or KCl is contraindicated and correction should be immediate, *i.e.*, when the arterial pH is greater than 7.55, and in the presence of hepatic encephalopathy, cardiac arrhythmia, digitalis cardiotoxicity, or altered mental status. The amount of HCl, given as 0.1 or 0.2 M solutions, needed to correct alkalosis is calculated by the formula: 0.5 × Body weight (kg) × Desired decrement in plasma bicarbonate (mEq/L); continuing losses must also be replaced. The use of 50% of body weight as the volume of distribution of infused protons relates mainly to the prior buffering of alkali including those in intracellular sites; infused protons must restore these buffers as well as titrating extracellular bicarbonate. Because the goal of such therapy is to rescue the patient from severe alkalosis, it is usually prudent to plan to initially restore the plasma bicarbonate concentration halfway toward normal. HCl must be given through a catheter placed in the vena cava or a large tributary vein. The proper placement of the catheter should be confirmed radiographically because leakage of HCl can lead to sloughing of perivascular tissue; in the mediastinum, this could be a catastrophe. Rates of infusion up to 25 mEq/h have been reported. These patients are best managed in an intensive care unit with frequent measurement of arterial blood gases and electrolytes.

NH_4Cl is an alternative, which may be given into a peripheral vein; its rate of infusion should not exceed 300 mEq/24 h. NH_4Cl is contraindicated by the presence of renal or hepatic insufficiency. In concurrent renal failure, azotemia would be worsened and, in hepatic failure, acute ammonia intoxication with coma could result. Lysine or arginine HCl should be avoided because they have been associated with dangerous hyperkalemia.

If GFR is adequate (serum creatinine <4 mg/dl), the use of acetazolamide 250 to 500 mg daily, which produces a diuresis of primarily $NaHCO_3$ by inhibition of carbonic anhydrase, can be considered. When high sodium excretion must be maintained or if a high serum potassium is present, acetazolamide is particularly useful. Natriuresis can be sustained while progressive metabolic alkalosis is avoided. If hyperkalemia is absent, KCl should be concurrently administered because of the high likelihood of developing hypokalemia during the ensuing alkaline diuresis.

When the kidney is incapable of responding to chloride repletion or dialysis is necessary for the control of renal failure, exchange of bicarbonate for chloride by hemodialysis or peritoneal dialysis will effectively correct metabolic alkalosis. The usual dialysates for both peritoneal dialysis and hemodialysis, which contain high concentrations of bicarbonate or its metabolic precursors, must be modified in these circumstances. In an emergency, peritoneal dialysis can be performed against sterile solutions of 150 mEq/L NaCl with appropriate maintenance of plasma potassium, calcium, and magnesium concentrations by intravenous infusion.

Additional therapeutic approaches are needed in certain specific clinical situations associated with chloride-depletion metabolic alkalosis. In the presence of pernicious vomiting or the need for the continual removal of gastric secretions, metabolic alkalosis will continue to be generated and replacement of preexisting deficits will be impeded by these losses. In such circumstances, the administration of a proton pump inhibitor, such as omeprazole, will blunt gastric acid production. Antiemetics may also be helpful. Proton pump inhibitors have also been used effectively to blunt the acid loss that occurs with gastrocystoplasty.

Congenital chloridorrhea is responsive to continued repletion of fluid, chloride, and potassium losses by supplementation of the dietary intake, whereas antidiarrheal agents are largely ineffective. Reduction in gastric HCl production by proton pump inhibition has been shown to aid in the maintenance of chloride balance (41). Villous adenomas require surgical removal.

Chloride-Resistant Alkaloses

When potassium depletion is associated with a mild-to-moderate metabolic alkalosis, oral KCl 40 to 60 mEq four or five times per day usually will suffice for correction. If, how-

ever, a cardiac arrhythmia or generalized weakness is present, intravenous KCl may be given at rates as high as 40 mEq/h in concentrations not to exceed 60 mEq/L. These very high rates should be used only when life-threatening situations are encountered. The patient should be monitored by electrocardiogram and frequent determinations of plasma potassium concentration because muscle uptake of potassium may initially be diminished by downregulation of muscle Na,K-ATPase. Glucose should be omitted initially from the solution used to administer potassium because stimulated insulin secretion may cause plasma potassium concentration to decrease even further. However, once potassium repletion has begun, the presence of glucose in the infusion will facilitate cellular potassium repletion. Because nephropathy due to potassium depletion may impair free water excretion, plasma sodium should be monitored, particularly if hypotonic fluids are administered.

When mineralocorticoid excess is the proximate cause, therapy is directed at either removal of the source or its blockade. Potassium-sparing diuretics, specifically spironolactone with hyperaldosteronism, will effectively reverse the adverse effects of mineralocorticoid excess on sodium, potassium, and bicarbonate excretion. Restriction of sodium and the addition of potassium to the diet will also ameliorate the alkalosis and the hypertension. Correction of the potassium deficit reverses the alkalinizing effects, but elimination of aldosterone excess is essential to permanent correction. In glucocorticoid-suppressible hyperaldosteronism, dexamethasone (0.25 mg mornings and 0.75 mg evenings) is the agent of choice to suppress ACTH secretion.

Many primary disorders of mineralocorticoid excess are definitively treated by tumor ablation. ACTH-secreting pituitary tumors may be removed by trans-sphenoidal resection or irradiation. With adrenal tumors, adrenalectomy, either unilateral or bilateral as appropriate, may be curative. In the ectopic ACTH syndrome, the ideal treatment of the secreting tumor can rarely be accomplished. In this instance and in metastatic adrenal tumors, metyrapone, which inhibits the final step in cortisol synthesis, or aminoglutethimide, which inhibits the initial step in steroid biosynthesis, will blunt the myriad manifestations of hypercortisolism. In those disorders in which curative surgery cannot be carried out, mitotane (o,p-DDD), which produces selective destruction of the zona fasiculata and reticularis and leaves aldosterone production intact, or cisplatin has also been used to control effectively many of the manifestations of the disease. However, to the extent that severe fluid and electrolyte disturbances are due solely to aldosterone production, mitotane may not suffice when hypokalemic alkalosis is present; metyrapone or aminoglutethimide would be better choices. Detailed discussion of the use of these drugs is beyond the scope of this review.

In BS and GS syndromes, the principal goal of therapy is to minimize urinary potassium loss. In BS, converting enzyme inhibitors, which reduce angiotensin II production and decrease aldosterone secretion, have been shown to be effective and should be tried first (42). Because renal prostaglandin production is increased in BS and may contribute to sodium, chloride, and potassium wasting, prostaglandin synthase inhibitors may ameliorate, but usually will not completely correct, the hypokalemic alkalosis. Magnesium depletion, which may also increase urinary potassium wasting, should be corrected. However, the degree to which magnesium repletion corrects alkalosis is uncertain, and magnesium salts often produce an unacceptable degree of gastrointestinal irritation that may compound the patient's problems.

In GS, potassium-sparing diuretics, such as amiloride 5 or 10 mg daily, triamterene 100 mg twice a day, or spironolactone 25 to 50 mg four times a day, will blunt the urinary losses but dietary potassium supplementation may also be needed. When causative, licorice intake or carbenoxolone should be stopped. In Liddle syndrome, amiloride is a reasonable first choice.

Miscellaneous

In the milk-alkali syndrome, cessation of alkali ingestion and the calcium sources (often milk and calcium carbonate), and chloride and volume repletion for the commonly associated vomiting, usually will lead to the prompt resolution of these abnormalities.

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