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Pharmacologically-Induced Metabolic Acidosis

A Review

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Abstract

Metabolic acidosis may occasionally develop in the course of treatment with drugs used in everyday clinical practice, as well as with the exposure to certain chemicals. Drug-induced metabolic acidosis, although usually mild, may well be life-threatening, as in cases of lactic acidosis complicating antiretroviral therapy or treatment with biguanides. Therefore, a detailed medical history, with special attention to the recent use of culprit medications, is essential in patients with acid-base derangements. Effective clinical management can be handled through awareness of the adverse effect of certain pharmaceutical compounds on the acid-base status. In this review, we evaluate relevant literature with regard to metabolic acidosis associated with specific drug treatment, and discuss the clinical setting and underlying pathophysiological mechanisms. These mechanisms involve renal inability to excrete the dietary H^+ load (including types I and IV renal tubular acidoses), metabolic acidosis owing to increased H^+ load (including lactic acidosis, ketoacidosis, ingestion of various substances, administration of hyperalimentation solutions and massive rhabdomyolysis) and metabolic acidosis due to HCO_3^- loss (including gastrointestinal loss and type II renal tubular acidosis). Determinations of arterial blood gases, the serum anion gap and, in some circumstances, the serum osmolar gap are helpful in delineating the pathogenesis of the acid-base disorder. In all cases of drug-related metabolic acidosis, discontinuation of the culprit medications and avoidance of readministration is advised.

Metabolic acidosis is a frequently encountered acid-base disturbance in hospitalized patients. It is characterized by a low arterial pH, a reduced serum HCO_3^- concentration and a compensatory decrease in the arterial partial pressure of carbon dioxide (PCO_2).[1] Taking into account the reaction of H^+ with the primary extracellular buffer serum bicarbonate (HCO_3^-), i.e. $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$, it is clear that metabolic acidosis occurs because of an increase in H^+ or decrease in HCO_3^-. Specifically, metabolic acidosis is caused by an inability of the kidney to excrete dietary H^+ load (e.g. because of renal failure, types I and IV renal tubular acidosis [RTA]) or an increase in H^+ generation, due to either addition of H^+ (e.g. lactic acidosis, ketoacidosis, massive rhabdomyolysis and ingestion of toxins such as ethylene glycol, methanol [methyl alcohol] or salicylates) or to gastrointestinal (e.g. diarrhoea, pancreatic or intestinal fistulas) and renal losses (type II RTA) of HCO_3^-.[1]

An approach to metabolic acidosis includes detailed history taking, physical examination and determinations of arterial blood gases, the serum anion gap and, in some circumstances, the serum osmolar gap [defined as the difference between measured and calculated serum osmolality] (figures 1 and 2).[1,2]

The symptoms of metabolic acidosis are mainly those of the underlying disorder.[2] Compensatory hyperventilation (i.e. Kussmaul breathing) is an important clinical sign and is often misinterpreted as a primary respiratory disorder.[2] Thus, when a dyspnoeic patient has normal cardiopulmonary examination findings, except for tachypnoea and tachycardia, a systemic acidosis should be considered. Drugs not infrequently represent a cause of metabolic acidosis and play a significant role in clinical presentation, evolution of the disease and therapeutic intervention.[3] In fact, drug-induced metabolic acidosis, although usually mild, may be

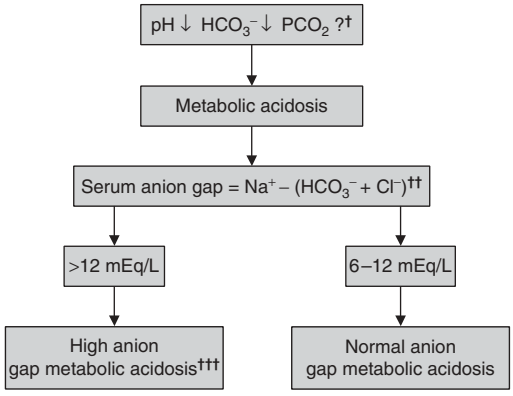

Fig. 1. Diagnostic approach to patients with metabolic acidosis. † In a pure metabolic acidosis, the arterial partial pressure of carbon dioxide (PCO_2) is appropriately decreased because of respiratory compensation [Winter's formula: $PCO_2 = (HCO_3^-$ [serum bicarbonate] $\times 1.5) + 8 \pm 2$, is an accurate way to calculate the expected PCO_2]. If PCO_2 is not appropriately decreased, a superimposed respiratory acidosis should be suspected. If PCO_2 is lower than anticipated, a superimposed respiratory alkalosis should be considered. †† In hypoalbuminaemic states, the corrected serum anion gap should be determined by adding 2.5 mEq/L to the calculated serum anion gap for every 1 g/dL decrement in serum albumin from normal value (assumed to be 4 g/dL). ††† In a patient with otherwise unexplained high anion gap metabolic acidosis, the serum osmolar gap should be calculated. In such cases, a high serum osmolar gap should be considered as an indication of methanol, ethylene glycol and paraldehyde intoxication or ingestion of propylene glycol-containing drugs. Note: The most widely used formula for calculating serum osmolality is 2 [Na^+] (mmol/L) + blood urea nitrogen (mg/dL)/2.8 + glucose (mg/dL)/18. Osmolar gap is defined as the difference between measured and calculated serum osmolality (normal range 5–10 mOsm/kg H_2O).

severe or even fatal (e.g. lactic acidosis due to antiretroviral therapy or treatment with biguanides). Physicians should be aware of this potentially life-threatening iatrogenic condition in terms of its incidence, prevalence, predisposing factors and clinical manifestations, in order to ensure that an early diagnosis can be made.

In this review, we evaluate the relevant literature with regard to metabolic acidosis associated with specific drug treatment, and discuss the clinical setting and underlying pathophysiological mechanisms.

1. Pathophysiological Aspects of Metabolic Acidosis

Maintenance of systemic arterial pH between 7.35 and 7.45 is required for normal cellular function, since even small fluctuations in the H^+ concentration have important effects on the activity of cellular enzymes[1,2] This is achieved by extracellular and intracellular buffers, together with respiratory and renal regulatory mechanisms. Control of both PCO_2 and HCO_3^- stabilizes the arterial pH by excretion or retention of acid or alkali. PCO_2 is regulated by the rate of alveolar ventilation. Hyperventilation increases CO_2 excretion and lowers the PCO_2, whereas hypoventilation diminishes CO_2 excretion, raising PCO_2. It should be emphasized that CO_2 acts as an acid in the body by combining with water to form H_2CO_3 according to the following reaction: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$.[1,2]

Under normal conditions, daily production of CO_2 (approximately 15 000 mmol) and its excretion by the lungs is matched, maintaining PCO_2 at 40 mmHg. Primary changes in PCO_2 induce acidosis (PCO_2 >40 mmHg) or alkalosis (PCO_2 <40 mmHg). Conversely, primary changes in serum HCO_3^- can cause compensatory (secondary) changes in ventilation that blunt the alterations in blood pH that would occur otherwise. It should be pointed out that these compensatory changes in PCO_2 can easily be misinterpreted or even overlooked when venous blood is sampled, given that the PCO_2 is 7–8 mmHg higher in venous blood than in arterial blood.

The kidney reabsorbs all of the filtered HCO_3^- and generates new HCO_3^- in the collecting duct.[1,2] Reabsorption of filtered HCO_3^- occurs in the proximal tubule (85–90%), in the thick ascending limb of the loop of Henle (10%) and the remainder in the distal nephron. Reabsorption of filtered HCO_3^- is essential for the maintenance of acid-base balance, given that the loss of HCO_3^- in the urine is equivalent to the retention of H^+ (both H^+ and HCO_3^- being derived from the dissociation of H_2CO_3).[1,2] A normal diet produces 50–100 mEq of H^+ per day as non-volatile sulphuric acid from amino acid catabolism, non-metabolized organic acid, and phosphoric and other acids. These H^+ ions are initially buffered by HCO_3^- and cellular and bone buffers to minimize the fall in extracellular pH. However, acid-base balance is restored by urinary H^+ excretion, which regenerates the HCO_3^- lost in the original buffering reaction. Indeed, the dietary

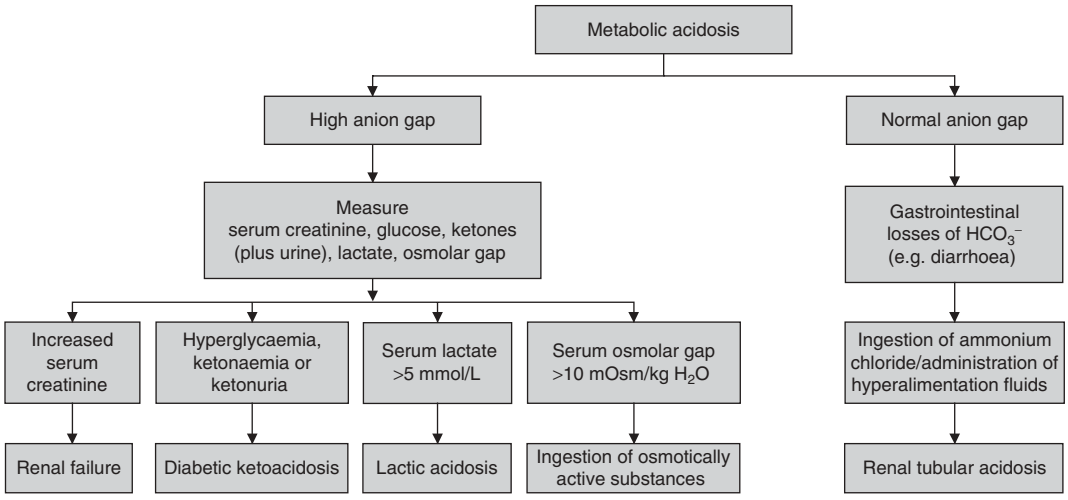

Fig. 2. Algorithm for assessing metabolic acidosis according to the anion gap.

acid load is excreted by the secretion of H^+ in the collecting duct. In the tubular lumen, these H^+ ions are combined either with HPO_4^{2-} (to form $H_2PO_4^-$ in a process called titratable acidity) or with NH_3 (to form NH_4^+). These processes are of paramount importance regarding the maintenance of acid-base balance, taking into consideration the extremely low rate of free H^+ excretion.[1,2]

In summary, the response of the body to an elevation of arterial H^+ concentrations involves four processes: extracellular buffering (HCO_3^- is the most important buffer in the extracellular fluid), intracellular and bone buffering, respiratory compensation and renal excretion of the H^+ load. Of these, the first three act initially until the definitive restoration of the acid-base balance is achieved by renal excretion of the excess H^+.

1.1 Serum Anion Gap

The anion gap is used to aid in the differential diagnosis of metabolic acidosis. The anion gap is equal to the difference between the serum concentrations of the major measured cations ($Na^+ + K^+$) and the major measured anions ($Cl^- + HCO_3^-$), i.e. the anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$.[1,2] However, given that the concentration of K^+ is relatively low compared with the other elements of the electrolyte profile (Na^+, Cl^-, HCO_3^-) this variable is usually ignored in the calculation of the anion gap, which is generally given as $Na^+ - (Cl^- + HCO_3^-)$.[1,2] In addition to being equal to the difference between measured cations and anions, the anion gap is also equal to the difference between unmeasured anions (anionic proteins, inorganic phosphate, sulphate and organic anions) and cations (calcium, magnesium and cationic proteins), i.e. the anion gap = unmeasured anions – unmeasured cations.[1,2]

Under normal circumstances, the bulk (approximately 80%) of the serum anionic gap is attributed to the anionic charges on circulating proteins. Taking into account that albumin is the most abundant circulating protein, it is clear that variability in the serum albumin level contributes to the biological variability of the serum anion gap. In fact, for each 1 g/dL reduction in serum levels of albumin, the serum anion gap is decreased by about 2.3–2.5 mEq/L.[4,5] Thus, in hypoalbuminaemic states, the corrected serum anion gap should be determined by adding 2.5 mEq/L to the calculated serum anion gap for every 1 g/dL decrement in serum albumin from normal value (assumed to be 4 g/dL).[6]

There are two major categories of clinical metabolic acidosis: high anion gap (anion gap >12 mEq/L [>16 mEq/L when K^+ is considered]), such as in lactic acidosis, ketoacidosis, renal failure,

massive rhabdomyolysis and following ingestion of toxins (e.g. ethylene glycol, methanol, salicylates) and normal anion gap or hyperchloraemic acidosis (anion gap 6–12 mEq/L), due to gastrointestinal (e.g. diarrhoea, pancreatic or intestinal fistulas) and renal (type II RTA) loss of HCO_3^-, RTA types I and IV, ingestion of ammonium chloride and administration of hyperalimentation fluids (figure 2).[1,2,7,8]

Calculation of the anion gap not infrequently fails to identify the extra unmeasured anions or detect complex metabolic acid-base disorders.[4,9,10] It has also been proposed that the anion gap is an insensitive screen for mild to moderate organic acidosis.[11] Therefore, the ratio of the change in the unmeasured anion concentration to the change in serum HCO_3^- concentration is used to evaluate more accurately metabolic acid-base disorders, specifically to detect complex acid-base disturbances in patients with some component of high anion gap metabolic acidosis.[12,13] However, in the majority of studies, calculation of the ratio of the change in the unmeasured anion concentration to the change in serum HCO_3^- concentration is based on the mean normal values for the anion gap and HCO_3^- concentration, instead of the actual normal values of individual patients; this may have an important impact on the computation of the ratio and the derived conclusions. Thus, strict recommendations that apply to all patients cannot be made. The ratio of the change in the unmeasured anion concentration to the change in serum HCO_3^- concentration in an uncomplicated high anion gap metabolic acidosis should be between 1 and 2.[14] Values lower than 1 : 1 indicate mixed normal and high anion gap acidosis, as might occur in patients with chronic kidney disease presenting with diarrhoea. On the other hand, a value above 2 : 1 suggests coexisting metabolic alkalosis (e.g. in patients presenting with vomiting).[14]

Taking into consideration the above-mentioned limitations, a physicochemical approach, originally proposed by Stewart, has been claimed to be more precise, particularly in patients hospitalized in intensive care units.[15-18] While gaining support, this approach has not yet been widely adopted in everyday clinical practice, since, to some degree at least, computerized data entry and calculation are required. Moreover, when the corrected anion gap is utilized, the Stewart approach is not associated with any diagnostic or prognostic advantages.[19] Consequently, taking into account the above-mentioned caveats, the anion gap should be considered an effective and inexpensive tool for detecting or suspecting the presence of various disorders.

2. Drug-Related Metabolic Acidosis Due to Renal Inability to Excrete the Dietary H^+ Load

2.1 Reduced NH_4^+ Production Due to Renal Tubular Acidosis (RTA) Type IV (Hypoaldosteronism)

Type IV RTA is characterized by hyperkalaemic, hyperchloraemic and normal anion gap metabolic acidosis (tables I and II). The defect is aldosterone deficiency or antagonism, which impairs distal renal Na^+ reabsorption and K^+ and H^+ excretion. The metabolic acidosis is also due in part to hyperkalaemia, as evidenced by correction of the acidaemia when the serum K^+ concentration is normalized.[20,21] Indeed, in hyperkalaemic states, K^+ moves into cells and H^+ moves out. The ensuing intracellular alkalosis may then account for the associated reductions in HCO_3^- reabsorption and NH_4^+ excretion by the renal tubular cells.[22] Thus, a reduction in net acid excretion takes place, leading to retention of some of the daily acid load and subsequent development of metabolic acidosis.

Several drugs have been implicated as culprits of hypoaldosteronism and hyperkalaemia due to different pathogenetic mechanisms, which involve (i) impaired release of renin by NSAIDs, β-adrenoceptor antagonists (β-blockers), ciclosporin and tacrolimus; (ii) renin-angiotensin-aldosterone system blockade by renin inhibitors, ACE inhibitors and angiotensin II type 1 receptor antagonists; (iii) impaired aldosterone metabolism by including heparin and ketoconazole; and (iv) blockade of aldosterone receptors by spironolactone and eplerenone. Furthermore, K^+-sparing diuretics, such as amiloride and triamterene, and two antibacterials, namely trimethoprim (commonly administered in

Table I. Principal causes and pathogenesis of drug-induced metabolic acidosis

Renal inability to excrete the dietary H^+ load
Reduced NH_4^+ production due to type IV renal tubular acidosis (hypoaldosteronism)
K^+-sparing diuretics (spironolactone, eplerenone, amiloride, triamterene), cotrimoxazole, ACE inhibitors, angiotensin II receptor type 1 antagonists, renin inhibitors, NSAIDs, ciclosporin, tacrolimus, heparin
Reduced H^+ secretion due to type I (distal) renal tubular acidosis
Amphotericin B, lithium carbonate, methicillin (meticillin), foscarnet, ifosfamide, toluene
Increased H^+ load
Lactic acidosis: biguanides, antiretroviral therapy (nucleoside reverse transcriptase inhibitors: zidovudine, stavudine, didanosine, lamivudine), linezolid, isoniazid, propylene glycol-containing drugs (lorazepam, diazepam, etomidate, pentobarbital, nitroglycerin), propofol, adrenergic stimulants (β_2-adrenoceptor agonists, theophylline, caffeine), alcohol (ethanol), nalidixic acid, overdose, HMG-CoA reductase inhibitors (statins), antibacterial-induced D-lactic acidosis, niacin
Ketoacidosis: alcohol, salicylates, atypical antipsychotic drugs (clozapine, olanzapine, risperidone, aripiprazole, quetiapine)
Ingestion of various substances: ethylene glycol, methanol (methyl alcohol)/formaldehyde, salicylates, paraldehyde, sevelamer (hydrochloride), sulfur, toluene, chlorine gas, ammonium chloride, Omnicide® (contains glutaraldehyde), hyperalimentation fluids
'Pyroglutamic acidaemia': paracetamol (acetaminophen), flucloxacillin, netilmicin, vigabatrin
Hyperalimentation solutions
Massive rhabdomyolysis: lipid-lowering drugs (statins, fibric acid derivatives), alcohol, illicit agents (heroin, cocaine), propofol
HCO_3^- loss
Gastrointestinal HCO_3^- loss: cholestyramine (colestyramine), laxative abuse
Renal loss of HCO_3^- due to type II (proximal) renal tubular acidosis: carbonic anhydrase inhibitors, ifosfamide, aminoglycosides, expired tetracycline, streptozocin, azacitidine (antimetabolites), mercaptopurine, valproic acid, ranitidine, lead, cadmium, mercury, antiretroviral drugs, propylene glycol-containing drugs
Miscellaneous
Hyperchloraemic acidosis due to rapid saline administration, niacin

combination with sulfamethoxazole as cotrimoxazole) and pentamidine, interfere with the reabsorption of Na^+ and the excretion of K^+ and H^+ that occur in the late distal tubule, the connecting tubule and the cortical-collecting duct by closing the Na^+ channels, leading to hyperkalaemia and acidosis. It should be emphasized that the majority of the aforementioned drugs can cause metabolic acidosis;[23-33] however, to our knowledge, there are currently no reports of RTA associated with the use of β-blockers, pentamidine or ketoconazole.

The incidence of RTA varies widely among hyperkalaemic drugs. For example, it has been reported that as many as 50% (four of eight) renal graft recipients treated with tacrolimus developed RTA compared with 12.5% (one of eight) patients receiving ciclosporin.[30] In another study, tacrolimus therapy was associated with a greater likelihood of acidosis than ciclosporin (odds ratio for acidosis of 1.8 and 0.6, respectively).[31] Of note, although hyperkalaemia is frequently encountered in patients taking cotrimoxazole, RTA is relatively uncommon.[34] In a series of 1121 patients receiving cotrimoxazole, only one (<0.1%) exhibited RTA.[32] Finally, coadministration of more than one of the above-mentioned drugs is associated with an increased risk of hyperkalaemia and/or metabolic acidosis, especially in patients with impaired renal function.[33]

2.2 Reduced H^+ Secretion Due to Type I (Distal) RTA

Classic type I (distal) RTA is a hyperchloraemic, normal anion gap metabolic acidosis resulting from a selective deficiency in H^+ secretion in the distal nephron.

In addition to its other toxic renal effects, such as elevation of serum creatinine, albuminuria, nephrogenic diabetes insipidus (NDI) and hypokalaemia, the antifungal agent amphotericin B can induce RTA.[35,36] Amphotericin B induces RTA by increasing membrane permeability in the collecting duct, which results in back-diffusion of secreted H^+ ions, thereby limiting the excretion of acid.[37] RTA is a relatively uncommon adverse effect of amphotericin B. In a series of 194 patients with cryptococcal meningitis treated with amphotericin B (0.3 mg/kg/day) and flucytosine (150 mg/kg/day), only two patients (1%) developed RTA.[38]

Lithium, which is used to treat bipolar (manic depressive) disorders, has become the most frequent cause of drug-induced NDI. Indeed, NDI is evident in almost 50% of patients receiving prolonged lithium therapy.[39] Chronic tubulointerstitial nephropathy and hypercalcaemia

represent additional renal complications of lithium therapy.[40] Moreover, the tubular defect in the distal nephron can also impair the ability to maximally acidify the urine. The incomplete form of type I RTA, in which the urine pH is persistently above 5.3, but the extracellular pH and HCO_3^- concentration are within the normal range, is the most frequent manifestation associated with chronic lithium therapy.[41]

Type I RTA has also been reported following treatment with methicillin (meticillin)[42] and foscarnet.[43]

3. Drug-Related Metabolic Acidosis Owing to an Increased H^+ Load

3.1 Lactic Acidosis

Lactic acidosis is a high anion gap metabolic acidosis with increased serum lactate concentrations (>5 mEq/L) [table II].[1] Normally, there is a daily lactic acid production up to 20 mmol/kg. Most of this amount is derived from the metabolism of pyruvate, which is generated from glucose through the glycolytic pathway or from deamination of alanine. Conversion of lactate back into pyruvate (by the liver and, to a lesser degree, the kidney), which is further metabolized to either CO_2 plus H_2O or glucose, represents the chief pathway for its removal.[44] These reactions require both the entry of pyruvate into the mitochondria and intact oxidative metabolism. On the other hand, pyruvate is preferentially converted into lactate in the cytosol in the presence of mitochondrial dysfunction or tissue hypoxia.[45,46] Lactic acidosis is classified into two types: type A, which is characterized by increased lactate production (due mainly to altered reduction-oxidation reaction state favouring pyruvate conversion to lactate but also to increased pyruvate production or impaired pyruvate utilization); and type B, which represents diminished lactate utilization and involves impaired removal of lactate by oxidation or gluconeogenesis. Finally, any decrement in lactate clearance should be considered a contributing factor of lactate accumulation.[45-48]

Table II. Classification of drug-induced metabolic acidosis according to anion gap

Normal anion gap (hyperchloraemic acidosis)
Type IV renal tubular acidosis (hypoaldosteronism)
Type I (distal) renal tubular acidosis
HCO_3^- loss (gastrointestinal and/or renal loss)
Ingestion of ammonium chloride/administration of hyperalimentation fluids
High anion gap acidosis
Lactic acidosis
Ketoacidosis
Ingestion of various substances: ethylene glycol, methanol (methyl alcohol)/formaldehyde, salicylates, paraldehyde, sevelamer (hydrochloride), sulfur, toluene, chlorine gas
'Pyroglutamic acidaemia'
Massive rhabdomyolysis
High osmolar gap metabolic acidosis
Propylene glycol-containing drugs: lorazepam, diazepam, etomidate, pentobarbital
Ethylene glycol
Methanol/formaldehyde
Paraldehyde

3.1.1 Biguanides

Biguanides are used, either alone or in combination with other oral agents or insulin, in the treatment of patients with type 2 diabetes mellitus. The most serious adverse effect of biguanide use is lactic acidosis (tables I and II). The high incidence of phenformin-induced lactic acidosis, occurring in 1 of 4000 patients and with an associated mortality rate as high as 50%, led to the withdrawal of this drug from the US market in 1976.[3,49] However, it is still available in several countries, constituting a public health problem.

Metformin is the principal biguanide in clinical use. The primary action of metformin is on the liver, reducing hepatic gluconeogenesis.[50] Metformin is not indicated for patients with type 1 diabetes and is contraindicated in diabetic patients with serum creatinine levels ≥1.5 mg/dL, hepatic insufficiency, alcoholism, advanced age or severe tissue hypoxia. Lactic acidosis has been reported as an adverse effect of metformin but, in contrast to phenformin, is uncommon.[50] The mechanism of metformin-associated lactic acidosis (MALA) is complex and not well understood. Metformin binds to mitochondrial membranes and affects the electron transport system (increasing the concentration of reduced

nicotinamide adenine dinucleotide), resulting in inhibition of oxidative metabolism. Particularly when metformin concentrations are high (in cases of overdose or reduced metformin excretion due to impaired renal function), oxidative phosphorylation is diminished and aerobic metabolism switches to anaerobic metabolism supplying large quantities of lactate coupled with a reduced utilization of lactate because of suppression of hepatic gluconeogenesis.[51,52] The mortality rate of metformin-induced lactic acidosis remains high (30% in a recent study[53]), although lower than previously reported (50%).[54] MALA has been rarely reported as a result of metformin voluntary intoxication (suicide attempt).[55] The estimated incidence of MALA is 6.3 per 100 000 patient-years.[56] However, the majority of reported cases included patients with conditions that can induce lactic acidosis *per se* or patients in whom metformin was contraindicated (table III). Indeed, epidemiological evidence does not support an association between metformin use and lactic acidosis. Specifically, there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis or with increased levels of lactate, compared with other antihyperglycaemic treatments when risk factors for lactic acidosis have been excluded.[56] However, there are several case reports of MALA in the absence of contraindications to use of metformin.[57-62] Of note, in most of these cases an underlying condition induced acute renal failure, such as extracellular volume depletion due to gastrointestinal losses, use of combinations of potent nephrotoxic drugs or administration of radiocontrast agents.[57-61] Moreover, a drug overdose might have played a contributory role in the development of MALA development.[62] Consequently, metformin should be discontinued in patients who are seriously ill and in patients who have concurrent pathologies that predispose to acute renal impairment. Metformin therapy should be temporarily halted on the day of an imaging test and for 2 days following the injection of radiocontrast agents to avoid potential lactic acidosis if acute renal failure ensues.

3.1.2 Antiretroviral Therapy

Lactic acidosis has, on rare occasions, been associated with the use of highly active antiretroviral therapy, particularly nucleoside reverse transcriptase inhibitor (NRTI)-based regimens. The incidence of this serious adverse event varies from 1.3 to 10 cases per 1000 treated person-years, depending on the case definition used.[63] In contrast, the incidence of asymptomatic hyperlactaemia is as high as 20% in patients receiving NRTIs. While uncommon, NRTI-induced lactic acidosis is associated with a high mortality rate, ranging from 33% to 57%.[64] Hyperlactaemia and lactic acidosis caused by NRTIs are attributed to mitochondrial toxicity resulting from inhibition of the mitochondrial DNA polymerase

Table III. Predisposing factors for metabolic acidosis associated with certain medications

Medication	Predisposing factor						
	renal insufficiency	hepatic insufficiency	alcoholism	age/sex/pregnancy	severe underlying conditions (e.g. malnutrition, sepsis)	combination treatment	other conditions
Biguanides	Yes	Yes	Yes	Advanced age	Yes	Not known	Not known
Antiretroviral drugs	Yes	Co-infection with hepatitis B or C	Not known	Female sex/pregnancy	Not known	>1 antiretroviral drug	Low nadir CD4 cell count
Propylene glycol-containing drugs[a]	Yes	Yes	Yes	Age <4 years/ pregnancy	Yes	>1 propylene glycol-containing drug	Not known
Paracetamol (acetaminophen)	Yes	Yes	Yes	Female sex	Yes	Flucloxacillin, netilmicin, vigabatrin	Chronic ingestion

a Propylene glycol-containing drugs: lorazepam, diazepam, etomidate, pentobarbital, nitroglycerin, cotrimoxazole.

γ, which in turn leads to significantly decreased mitochondrial DNA levels. Specifically, mitochondrial toxicity consists of reduced oxidative phosphorylation, intracellular accumulation of lipids and elevation of lactic acid levels.[65] Although lactic acidosis appears to be a class effect complication of NRTIs, the risk is higher with didanosine, followed, in decreasing order, by stavudine and zidovudine.[66] Compared with monotherapy, patients receiving combination treatment, including didanosine with either tenofovir or stavudine, are at greater risk of developing lactic acidosis. Furthermore, female sex, pregnancy, low nadir CD4 cell count before starting NRTIs, impaired renal function and co-infection with hepatitis B or C have also been proposed as potential risk factors for this adverse effect (table III).[67,68]

In addition to lactic acidosis, antiretroviral therapy-induced acidosis could be attributed to either proximal or distal RTA.[69] Indeed, Fanconi's syndrome and proximal RTA have been reported in HIV-infected patients receiving tenofovir, abacavir, didanosine and acyclic nucleotide phosphonate analogues (cidofovir, high-dose adefovir).[69] Co-existence of Fanconi's syndrome and lactic acidosis has also been reported with co-administration of stavudine and lamivudine.[70]

3.1.3 Linezolid

Linezolid, the first member of a newly developed drug family (the oxazolidinones) is primarily active against aerobic Gram-positive pathogens, including penicillin-resistant pneumococci, methicillin-resistant staphylococci and enterococci (both *Enterococcus faecalis* and vancomycin-sensitive and -resistant *E. faecium*).[71] Linezolid exerts its bacteriostatic effect of inhibiting bacterial protein synthesis by preventing the fusion of 30S and 50S ribosomal subunits. Its primary toxicity is bone marrow suppression with long-term therapy, particularly involving the platelet line.[71] Linezolid-induced lactic acidosis caused by inhibition of mitochondrial protein synthesis (probably due to similarities between bacterial and mitochondrial ribosomes) has been reported.[72-74] Some authors have suggested that individuals with mitochondrial DNA polymorphisms A2706G and G3010A might be particularly susceptible to linezolid-associated lactic acidosis.[73,74] Lactic acidosis is mainly associated with prolonged linezolid therapy;[75] however, cases of lactic acidosis early in linezolid treatment have also been reported.[76] Simultaneous administration of isoniazid that can also induce lactic acidosis or selective serotonin reuptake inhibitors that diminish linezolid clearance by blocking P-glycoprotein activity may be possible reasons for early linezolid-associated lactic acidosis.[77] It is worth mentioning that the majority of cases of reported lactic acidosis due to linezolid therapy had a favourable outcome, even if presentation was severe with a pH as low as 7.02.[72]

3.1.4 Isoniazid

Isoniazid overdose (>30 mg/kg) produces a triad of coma, metabolic acidosis and seizures that are often refractory to traditional antiepileptics.[78] Isoniazid-associated metabolic acidosis is not infrequently severe and is attributed to lactate overproduction resulting from excessive muscular activity during a grand mal seizure.[78] Consequently, the diagnosis of isoniazid toxicity should be considered in any patient who presents with an unexplained metabolic acidosis and convulsions. Pyridoxine (vitamin B_6) comprises the cornerstone of therapy and the dose should be equivalent to the amount of isoniazid ingested.[79,80] It should be emphasized that ingestion of isoniazid in amounts of 80–150 mg/kg or more can be rapidly fatal.[81]

3.1.5 Propylene Glycol

Propylene glycol (1,2-propanediol) is a solvent in numerous pharmaceutical preparations (intravenous, oral and topical) and a major preservative and source of carbohydrates in processed foods.[82] Although the agent is generally considered to be safe, rapid and prolonged administration of large doses increases the risk of toxicity. Indeed, propylene glycol-containing drugs can induce a hyperosmolar, high anion gap metabolic acidosis that is life threatening if untreated. In the majority of cases, lorazepam, which contains the largest proportion of propylene glycol among these drugs, and etomidate have been implicated.[83-85]

For example, in a small, randomized study of hospitalized patients (n = 7) in a neurosurgical clinic who received continuous infusions of etomidate or pentobarbital, the incidence of high anion gap metabolic acidosis was 100% and 0%, respectively;[86] however, a case of pentobarbital-induced lactic acidosis has recently been reported.[87] In another study, Wilson et al.[83] showed that 4 (19%) of 21 patients who received propylene glycol-containing medications (lorazepam or diazepam) exhibited metabolic evidence of propylene glycol toxicity. Specifically, all four patients had either an elevation in the anion gap or a decrease in serum HCO_3^-, while serum lactic acid was increased in only one subject.

A hyperosmolar, high anion gap metabolic acidosis is rarely observed in patients receiving nitroglycerin, another propylene glycol-containing drug.[88] The hyperosmolarity with elevated osmolar gap can be ascribed to propylene glycol, which is a hyperosmolar substance. Moreover, the high anion gap metabolic acidosis is due to increased serum lactate concentration. In fact, approximately 55% of absorbed propylene glycol undergoes oxidation in the liver by alcohol dehydrogenase to pyruvate, lactate or acetate, while the remainder is removed via renal excretion.[89] Thus, impairment of hepatic and renal function is associated with increased susceptibility to propylene glycol-induced adverse effects. Co-administration of two propylene glycol-containing drugs (e.g. lorazepam and cotrimoxazole), alcohol abuse (ethanol and propylene glycol are metabolized by similar mechanisms), age <4 years and pregnancy represent risk factors for propylene glycol toxicity (table III).[83,84,90]

It should also be noted that propylene glycol is the vehicle of several preparations and in this form can cause a normal anion gap metabolic acidosis through proximal tubular injury.[91]

3.1.6 Propofol

Propofol is a short-acting intravenous anaesthetic agent used widely in adults and children for sedation and for the induction and maintenance of anaesthesia.[92] Metabolic acidosis (mainly lactic acidosis) has repeatedly been associated with propofol therapy. Bonhomme et al.[93] showed that the incidence of propofol-induced metabolic acidosis during intracranial surgery was 24% (7 of 29 patients). There was a linear correlation between the severity of metabolic acidosis and lactate levels (R^2 [coefficient of determination] = 0.32), total dose of propofol ($R^2 = 0.2$) and length of administration ($R^2 = 0.28$).[93] Similarly, the incidence of propofol-associated metabolic acidosis during noninvasive radiofrequency ablation for atrial flutter or fibrillation was reported to be 24% (13 of 55 patients).[94] However, in this study, the aetiology of metabolic acidosis was not provided (serum lactate and Cl^- are not measured). It should be emphasized that the diagnosis of metabolic acidosis in patients receiving propofol is of vital importance because it may be an early sign of the propofol infusion syndrome (PRIS). Although the clinical manifestations of this syndrome vary widely, it is characterized by severe metabolic acidosis, rhabdomyolysis, hyperkalaemia, acute renal failure, dyslipidaemias and progressive myocardial failure with dysrhythmias resulting in death (the mortality rate exceeds 80%).[95-97] PRIS is a rare complication that occurs mainly in severely ill patients, including those with sepsis and patients with serious head injury. Prolonged propofol administration (>48 hours) at high dosages (>4 mg/kg/h), concomitant use of catecholamine vasopressors or corticosteroids, age <18 years and inborn errors of mitochondrial fatty acid oxidation are considered the most important risk factors for PRIS.[95-97] It has been suggested that during states of increased metabolic demand, the reduced energy production related to an inhibitory action of propofol at the level of mitochondrial oxidative phosphorylation and lipid metabolism may lead to the development of PRIS.[98]

3.1.7 Adrenergic Stimulants

Lactic acidosis has also been described following treatment with agents that increase adrenergic activity (adrenergic stimulants), including β_2-adrenoceptor agonists, theophylline and caffeine.[99-101] The underlying pathophysiological mechanisms are not completely understood. It is known that excessive sympathetic activity increases glycogenolysis and lipolysis, leading

to increased pyruvate levels. Impaired pyruvate utilization via diminished pyruvate oxidation and/or inhibition of pyruvate dehydrogenase might also contribute to the development of lactic acidosis.[102] Additionally, it has been reported that in healthy people, β_2-agonists increase oxygen consumption (by increasing metabolic rate) and serum lactate levels.[103]

Lactic acidosis during acute asthmatic attacks deserves special attention. The disturbance increases both the sensation of dyspnoea and compensatory hyperventilation, causing clinical deterioration. It should be ascribed either to excessive respiratory muscle work, hypoxaemia and related liver ischaemia, or to treatment with β_2-agonists, theophylline and/or corticosteroids that enhance the sensitivity of β-adrenoceptors to sympathetic agents.[104] The latter could easily be misinterpreted as a sign of treatment failure and lead to inappropriate intensification of treatment. Therapy-associated lactic acidosis should be strongly suspected in patients with an asthmatic exacerbation in which dyspnoea deteriorates at the same time that bronchial obstruction improves.

Lactic acidosis due to β_2-agonists used as tocolytic therapy has also been described.[105]

3.1.8 Nalidixic Acid

Nalidixic acid overdose interfering with lactate metabolism may cause severe metabolic acidosis.[106,107] Indeed, a fatal case of lactic acidosis related to nalidixic acid treatment has been reported.[108]

3.1.9 HMG-CoA Reductase Inhibitors (Statins)

It has been suggested that HMG-CoA reductase inhibitors (statins), in two cases at least, may cause lactic acidosis by reducing coenzyme Q10 concentration, which plays a vital role in oxidative phosphorylation.[109,110] Thiamine deficiency and underlying hepatic disease may increase the risk of statin-related lactic acidosis.[109,110]

3.1.10 Antibacterial-Induced D-Lactic Acidosis

A unique form of lactic acidosis is observed in patients after either intestinal bypass surgery or small bowel resection. In these subjects, D-lactic acid is produced as a result of glucose and starch metabolism in the colon and is then absorbed into the systemic circulation.[1] Since D-lactate is not recognized by L-lactate dehydrogenase (the enzyme that catalyzes the conversion of the physiologically occurring L-lactate into pyruvate), acidaemia can result. In patients with short bowel syndrome, overproduction of D-lactic acid may occur due to overgrowth of Gram-positive anaerobes (e.g. lactobacilli), which are more able to produce D-lactate. By promoting the overgrowth of D-lactate-producing organisms, oral antibacterials such as tetracycline and metronidazole can cause D-lactic acidosis.[111,112]

3.2 Ketoacidosis

Ketosis results from a marked increase in free fatty acid release from adipocytes, with a resulting shift toward ketone body (acetoacetate, β-hydroxybutyrate and acetone) synthesis in the liver.[113] The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver. In particular, diminished activity of insulin increases lipolysis and the release of free fatty acids that, normally, are converted to triglycerides or very low-density lipoprotein in the liver. Moreover, enhanced secretion of glucagon alters hepatic metabolism to favour ketone body formation. Acetoacetate and β-hydroxybutyrate are strong acids that deplete the body's buffering system, leading to systemic acidosis.[113]

3.2.1 Alcohol (Ethanol)

Alcohol ingestion, especially when it is associated with poor carbohydrate intake, is often implicated in the aetiology of ketoacidosis (alcoholic ketoacidosis) by decreasing the insulin to glucagon ratio.[114] Furthermore, ethanol, by causing a direct increment in lipolysis, further increases the supply of free fatty acid. It appears that alcoholic ketoacidosis is not rare. In fact, alcoholic ketoacidosis was diagnosed in 20 (25.3%) of 79 alcoholic patients admitted to our department for causes related to alcohol abuse.[115] Of importance, alcoholic ketoacidosis is severe and not infrequently a fatal clinical

entity.[116] It is noteworthy that mild lactic acidosis may also be observed in alcoholic patients because of diminished lactate utilization resulting from impaired hepatic gluconeogenesis, while lactate production is usually normal.[117]

3.2.2 Antipsychotic Agents

Several reports suggest that use of atypical antipsychotic agents, such as clozapine, olanzapine, risperidone, aripiprazole and quetiapine, may be related to new-onset type II diabetes or exacerbation of pre-existing disease.[118-120] It appears that the risk of diabetes is more prominent with olanzapine than with other atypical agents.[121-123] Atypical antipsychotic drugs have also been associated with a small increase in the risk of diabetic ketoacidosis. However, Leslie and Rosenheck[121] showed that only 88 (0.2%) of 56 849 patients receiving atypical antipsychotic medications exhibited diabetic ketoacidosis. The causal link between diabetes and treatment with atypical antipsychotic drugs should be ascribed either to insulin resistance or to impairment of insulin secretion. Thus, patients with atypical antipsychotic drug-related diabetes could be divided into two subgroups:[124] (i) those that simulate typical patients with type II diabetes (gradual onset, weight gain and abdominal fat deposition), in whom increased insulin resistance is proposed to be the major underlying mechanism;[125] and (ii) a small percentage of patients with rapid emergence of diabetes after starting antipsychotic therapy in whom diabetic ketoacidosis occurs infrequently and in whom lack of insulin is possibly the underlying mechanism. Compared with the first subgroup, patients with ketoacidosis (the second subgroup) are younger, more often women than men and less overweight at baseline.[126-128]

3.3 Ingestion of Various Substances

3.3.1 Methanol (Methyl Alcohol)

Methanol intoxication occurs after accidental or suicidal oral ingestion of industrial solvents or cleaning and antifreeze liquids. Moreover, methanol is sometimes ingested intentionally by alcoholic patients as a substitute for ethanol, and may also be found as a contaminant in bootleg whisky. Methanol is metabolized to formaldehyde and then formic acid. Accumulation of these metabolites, particularly formic acid, is responsible for both symptoms and metabolic acidosis.[129,130] The diagnosis is based on the presence of severe metabolic acidosis with high anion and osmolar gap, and high serum methanol concentrations (figures 1 and 2 and table II).[129,130]

3.3.2 Ethylene Glycol

Ethylene glycol (commonly used in antifreeze) is metabolized to a variety of toxic metabolites (mainly oxalic acid and glycolic acid), resulting in a metabolic acidosis and severe damage to the CNS, heart, lungs and kidneys. The diagnosis is facilitated by recognizing oxalate crystals in the urine, the presence of an osmolar gap in the serum and a high anion gap acidosis (figures 1 and 2 and table II).[131] The diagnosis is confirmed, however, by demonstration of ethylene glycol in the serum. Ethylene glycol toxicity presenting with normal anion gap metabolic acidosis has also been reported.[132] It should be noted that an increased osmolar gap is a relatively nonspecific finding given that it is also observed in other high anion gap acidosis, including chronic, but not acute, renal failure (due to the retention of unidentified small solutes). If, however, the history is not compatible with lactic acidosis or ketoacidosis, a high serum osmolar gap (especially >25 mOsm/kg H_2O) is suggestive of either methanol (see section 3.3.1) or ethylene glycol intoxication.[132]

3.3.3 Paraldehyde

Paraldehyde can also produce severe metabolic acidosis; however, the organic acids responsible for an increased anion gap in paraldehyde intoxication have not been identified.[133,134]

3.3.4 Salicylates

Salicylate intoxication in adults usually causes respiratory alkalosis or a mixture of high anion gap metabolic acidosis and respiratory alkalosis; pure metabolic acidosis is unusual.[135] Once ingested, aspirin (acetylsalicylic acid) is rapidly converted to salicylic acid, its active moiety. Salicylic acid is readily absorbed from the stomach and small bowel. At therapeutic doses, salicylic acid is metabolized by the liver and eliminated in

2–3 hours. Therapeutic serum concentrations are 10–30 mg/dL and chronic ingestion can increase the half-life to >20 hours.[136] Clinical features of aspirin intoxication occur in most people with serum concentrations >40 mg/dL; severe acute intoxication may occur after a single ingestion of more than 200 mg/kg of salicylate.[135] Intoxication may also result from chronic excessive dosing over several days. In chronic intoxication, severe poisoning occurs at lower serum concentrations (particularly in elderly patients). At toxic concentrations, salicylates are metabolic poisons that affect a multitude of organ systems by uncoupling oxidative phosphorylation and interfering with the Krebs cycle.[137] Minor intoxication causes tinnitus, vertigo, nausea, vomiting and diarrhoea. As mentioned above, significant ingestions in adults result in respiratory alkalosis or a mixed metabolic acidosis and respiratory alkalosis (unless co-ingestion of a CNS depressant causes respiratory acidosis).[136] Respiratory alkalosis occurs through direct central stimulation. Uncoupling of oxidative phosphorylation leads to accumulation of organic acids (including lactic acid and ketoacids) and a metabolic acidosis with an elevated anion gap. Salicylic acid itself contributes only minimally to the measured anion gap (3 mEq/L with a 50 mg/dL serum concentration).[136] Of interest, salicylate-induced Fanconi's syndrome (without metabolic acidosis) has also been reported.[138]

Optimal management of salicylate poisoning depends on whether the exposure is acute or chronic.[136] Gastric lavage and activated charcoal (1 g/kg) are useful for acute ingestions but not in cases of chronic salicylism. Administration of HCO_3^- to raise plasma pH to between 7.45 and 7.5 induces urinary alkalinization, which in turn increases renal clearance. Urinary alkalinization must be used with caution in the presence of alkalaemia because of salicylate-induced hyperventilation. Salicylates can be removed by haemodialysis. Indications for haemodialysis include a serum concentration of >120 mg/dL acutely, or >100 mg/dL 6 hours post-ingestion, refractory acidosis, coma or seizures, non-cardiogenic pulmonary oedema, volume overload and renal failure. In chronic overdose, haemodialysis may be necessary for a symptomatic patient with a serum salicylate concentration >60 mg/dL.[136]

3.3.5 Sevelamer (Hydrochloride)

Metabolic acidosis, or worsening of pre-existing acidosis, has been reported in patients receiving long-term dialysis who are administered the acidotic agent sevelamer (hydrochloride).[139] Sevelamer contains multiple amines, which become partially protonated in the intestine and may exchange hydrochloride for HCO_3^- or phosphate or bile salts, leading to a decline in post-dialysis pH. It has been reported that the incidence of sevelamer-associated metabolic acidosis is as high as 22%.[140] Use of sevelamer carbonate, which does not decrease serum HCO_3^- concentrations, should be considered a more appropriate approach for patients with renal insufficiency in whom phosphate binders are required.[139]

3.3.6 Other Compounds

Sniffing of toluene, inhalation of chlorine gas and ingestion of elemental sulphur have rarely been associated with metabolic acidosis because of their metabolites, namely hippuric acid, hydrochloric acid and sulphuric acid, respectively.[141] Additionally, toluene exposure due to glue-sniffing has been considered a common cause of type 1 RTA in recreational drug abusers.[141]

The hepatic conversion of ammonium chloride into hydrochloride and urea can induce hyperchloraemic metabolic acidosis even in healthy individuals with normal renal function, especially when large doses are ingested.[142]

Ingestion of the disinfectant Omnicide® is associated with metabolic acidosis because of the metabolism of its component glutaraldehyde to semialdehyde and subsequently to glutaric acid.[143]

3.4 'Pyroglutamic Acidaemia'

High anion gap metabolic acidosis has frequently been described in patients with paracetamol toxicity.[144] This was generally attributed to lactic acidosis and kidney failure. However, in patients who have less severe toxicity and a history of long-term paracetamol ingestion, the anion gap cannot be explained. Paracetamol may

induce a high anion gap metabolic acidosis by depleting glutathione, thus leading to increased formation of glutamyl cysteine, which is then metabolized to pyroglutamic acid (5-oxoproline).[145] Long-term ingestion of paracetamol and female sex are associated with an elevated risk of metabolic acidosis. Pitt[146] measured urine 5-oxoproline excretion in patients who ingested paracetamol compared with control subjects. Urine 5-oxoproline excretion in the paracetamol group was >100-fold higher than that in the control group. Fenves et al.[147] reviewed 22 cases of 'pyroglutamic acidaemia' and showed that 18 patients (82%) were women and only one was not exposed to long-term paracetamol. It should be emphasized that paracetamol ingestion alone does not probably generate clinically significant 5-oxoprolinuria or metabolic acidosis. In most cases, synergistic interactions between paracetamol ingestion and multiple other factors exist.[148] All of these patients had underlying or preceding illnesses and most were malnourished. This probably depleted hepatic glutathione stores and undoubtedly increased the patients' susceptibility to the toxic effects of long-term paracetamol use. Many but not all of the patients had abnormal liver function tests. Several also had a history of chronic alcohol abuse, which is also known to reduce glutathione levels.[149] Acetylcysteine has been used with some effectiveness in patients with glutathione synthetase deficiency because it is thought to increase the low intracellular glutathione and cysteine concentrations.[150] In view of the low toxicity and theoretical benefit of acetylcysteine, its use seems reasonable in patients with metabolic acidosis related to paracetamol, but this is an issue for further investigation.

Although less often the case than with paracetamol, flucloxacillin, netilmicin and vigabatrin can also cause the same acid-base disorder via disturbance of the γ-glutamyl cycle, leading to elevated serum levels of 5-oxoproline.[147,151,152] Co-administration of paracetamol with these drugs, as well as malnutrition, severe sepsis, chronic alcohol abuse and diminished renal or hepatic function, may increase the risk of 5-oxoproline-related metabolic acidosis (table III).[153]

3.5 Administration of Hyperalimentation Solutions

The administration of hyperalimentation fluids has been implicated in the development of metabolic acidosis. It is known that the cationic amino acids, such as arginine and lysine, which are contained in excess in some of these solutions, are metabolized to neutral products. This process liberates H^+ ions, causing metabolic acidosis. The reduction in titratable acid excretion due to hypophosphataemia that is usually observed in starved patients after initiating feeding may also have a contributory role.[154] It has been reported that the incidence of metabolic acidosis is considerably higher in patients taking Cl^--based parenteral nutrition than in those taking an acetate-base regimen.[155] Renal insufficiency increases the risk of development of metabolic acidosis in this clinical setting.[155]

3.6 Massive Rhabdomyolysis

Massive rhabdomyolysis can, on rare occasions, induce elevated anion gap metabolic acidosis by releasing H^+ and organic anions from damaged cells.[156] Lipid-lowering agents (statins, fibric acid derivatives), alcohol, heroin (diamorphine) and cocaine are among the most frequently reported drugs and toxins that may be associated with rhabdomyolysis.[157]

4. Drug-Related Metabolic Acidosis Due to HCO_3^- Loss

4.1 Gastrointestinal HCO_3^- Loss

Cholestyramine (colestyramine) is an orally administered anion exchange resin used to bind bile acids in the bowel lumen. Its main indications include the treatment of hypercholesterolaemia and pruritus associated with obstructive or cholestatic jaundice.[158] Given that HCO_3^- competes with bile acids for binding sites on the resin, some intestinal HCO_3^- is taken up in exchange for Cl^-, leading to hyperchloraemic metabolic acidosis. Renal impairment, extracellular volume depletion and spironolactone administration have been associated with an increased risk of

cholestyramine-induced metabolic acidosis (tables I and II).[159,160]

It is well known that diarrhoeal states result in significant HCO_3^- losses, given that stool water is rich in HCO_3^-. Consequently, occult laxative abuse should be considered in any patient with a hyperchloraemic metabolic acidosis and/or chronic diarrhoea of unknown aetiology.[1]

4.2 Renal Loss of HCO_3^- Due to Type II (Proximal) RTA

Proximal RTA (type II) is a hyperchloraemic metabolic acidosis due to a selective defect in the ability of the proximal tubule to adequately reabsorb filtered HCO_3^- (tables I and II).[161] The defect in HCO_3^- reabsorption occurs either alone or as part of Fanconi's syndrome, with proximal tubular reabsorption of phosphate, glucose, amino acids and uric acid being impaired. Consequently, in this setting, hypophosphataemia, hypouricaemia, aminoaciduria and/or glucosuria (in the absence of increased serum glucose levels) may accompany metabolic acidosis.[161]

4.2.1 Carbonic Anhydrase Inhibitors

Acetazolamide and other carbonic anhydrase inhibitors are among the most common causes of type II RTA in adults. In a series of 27 elderly patients with glaucoma who received 250–1000 mg of acetazolamide daily, 15 patients (55%) developed metabolic acidosis.[162] Specifically, four patients (14.8%) exhibited mild acidosis (pH >7.29 to ≤7.31), ten patients (37%) had moderate acidosis (pH >7.20 to ≤7.29) and one patient (3.7%) had severe metabolic acidosis (pH 7.15).[162] Metabolic acidosis in response to topical eye drops of the carbonic anhydrase inhibitor brinzolamide has also been reported.[163]

Carbonic anhydrase inhibitors provoke metabolic acidosis by inhibiting the reabsorption of HCO_3^- ions from renal tubules. Renal function impairment, diabetes, coadministration of nephrotoxic drugs and advanced age are more frequently implicated in life-threatening metabolic acidosis during acetazolamide therapy.[164-167]

Topiramate, an agent used for seizure and migraine prophylaxis, has been reported to induce proximal RTA by inhibiting the carbonic anhydrase enzyme.[168] Indeed, in one study, almost half (48%) of the patients receiving topiramate exhibited some degree of metabolic acidosis.[169] Topiramate-associated metabolic acidosis was shown to be dose-dependent and usually mild; however, it may become clinically significant in the presence of renal insufficiency or other predisposing conditions.[169]

4.2.2 Ifosfamide

Ifosfamide is a chemotherapeutic agent with considerable renal adverse effects. Toxicity involves mainly proximal (type II RTA) and distal renal tubules (type I RTA and NDI).[170] In a series of 75 patients receiving ifosfamide, the incidence of acidosis and/or Fanconi's syndrome was 7%.[171] Moreover, a report of 22 children completing a course of ifosfamide documented three cases (14%) of proximal RTA.[172] It should be noted that concurrent administration of another nephrotoxic agent and increased total dose of the drug represent risk factors for ifosfamide nephrotoxicity. Clinically significant toxicity appears to occur at a total dose above 100 g/m^2.[172] It has been suggested that chloroacetaldehyde, a metabolite of ifosfamide, may be responsible for this nephrotoxicity. It appears that chloroacetaldehyde causes kidney dysfunction, glutathione depletion and lipid peroxidation.[173] Concurrent use of mesna (sodium 2-mercaptoethanesulfonate), a synthetic thiol compound that detoxifies reactive ifosfamide metabolites, reduces the incidence of ifosfamide-induced haemorrhagic cystitis; however, it provides limited protection against chloroacetaldehyde renal adverse effects.[174]

4.2.3 Other Compounds

Aminoglycosides can also induce proximal tubular damage, Fanconi's syndrome and, rarely, RTA.[175] Furthermore, prolonged administration and high doses are associated with an increased risk of these disorders.

Long-term occupational or environmental exposure to a number of heavy metals (lead, cadmium, mercury) may result in Fanconi's syndrome and RTA.[176-178]

Expired or improperly stored tetracycline, as well as streptozocin, azacitidine (antimetabolites), mercaptopurine, valproic acid and ranitidine, are also associated with Fanconi's syndrome and RTA.[179-184]

5. Miscellaneous Causes of Drug-Induced Metabolic Acidosis

Administration of HCO_3^--free solutions may induce mild hyperchloraemic metabolic acidosis by causing rapid volume expansion; however, dilutional acidosis has minor clinical significance, given that rapid intracellular and bone buffering briskly return the serum HCO_3^- concentration towards normal.[185]

By inducing insulin resistance and increased glucagon secretion, niacin can cause metabolic acidosis that may be life threatening. Indeed, niacin overdose has been reported to provoke severe metabolic acidosis (pH 6.9, HCO_3^- 6.3 mmol/L).[186] In addition, lactic acidosis has been documented as complicating high-dose niacin and co-ingestion of niacin at conventional doses with alcohol.[187,188]

6. Conclusions

Metabolic acidosis may occasionally develop in the course of treatment with drugs used in everyday clinical practice as well as with exposure to certain chemicals. It should be noted that drug-induced metabolic acidosis, although usually mild, may be severe or even fatal, as in the occasion of lactic acidosis caused by biguanide and antiretroviral therapy. A detailed history of medications received is fully warranted as part of the diagnostic approach to patients presenting with unexplained metabolic acidosis. Determinations of arterial blood gases, the serum anion gap and, in some circumstances, the serum osmolar gap are helpful in delineating the pathogenesis of the acid-base disorder. Discontinuation of culprit medications and avoidance of readministration is advised. Awareness of the adverse effect of certain pharmaceutical compounds on the acid-base balance facilitates rational clinical management.

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