Drug-induced metabolic acidosis

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Summary

Drug causes of metabolic acidosis are numerous and their mechanisms are diverse. Broadly, they can cause metabolic acidosis with either a normal anion gap (e.g. drug-induced renal tubular acidosis) or an elevated anion gap (e.g. drug-induced lactic acidosis or pyroglutamic acidosis). This review describes the drugs that can cause or contribute to metabolic acidosis during therapeutic use, the mechanisms by which this occurs, and how they may be identified in practice.

Introduction

Acidosis and acidaemia

Acidosis is a pathological process defined as a tendency to accumulate hydrogen ions (H^+) in the body. Acidosis may cause **acidaemia,** which is the accumulation of H^+ in blood resulting in a low serum pH (conventionally defined as below pH 7.35). The terms are often used interchangeably, although this overlooks some important conceptual distinctions:

1. Whereas acidaemia is always the result of acidosis, not all patients with acidosis have acidaemia. This is because the effect of acidosis (the process) on serum pH (the measurable abnormality) may be confounded by physiological buffering and compensatory mechanisms, and by co-existing acid-base disorders.
2. Whereas acidaemia is measured only in blood, acidosis affects all body compartments, and it may not be distributed evenly between them. For example, the acidosis may be more severe within cells than in the blood.
3. Whereas acidaemia is measurable, the presence and severity of acidosis is inferred from the clinical context as well as the serum acid-base status.

Metabolic and respiratory acidosis

Acidosis and acidaemia are classified as **metabolic** or **respiratory** according to the primary disturbance.

- **Metabolic acidosis** is due to increased production or reduced excretion of non-volatile acid. **Metabolic acidaemia** is the measurable manifestation of this, defined by a low serum pH and low serum bicarbonate concentration ($[HCO_3^-]$). However, due to buffering and compensation, and in mixed acid-base disturbances, the serum pH may be normal. Metabolic acidosis is then inferred from the serum $[HCO_3^-]$, taking account of the clinical context. For example, the finding of a low-normal $[HCO_3^-]$ in a patient with chronic hypercapnic respiratory failure who usually has a high serum $[HCO_3^-]$ suggests an acute process causing metabolic acidosis.
- **Respiratory acidosis** results from insufficient respiratory excretion of volatile acid (carbonic acid, as carbon dioxide). The corresponding measurable abnormality in arterial blood is **respiratory acidaemia**, defined by a low serum pH and elevated partial pressure of carbon dioxide (pCO_2).

Serum anion gap in metabolic acidosis

The anion gap describes the excess of 'unmeasured anions' relative to 'unmeasured cations' in serum.[1] It is inferred from the excess of 'measured cations' (Na^+ and K^+) to 'measured anions' (HCO_3^- and Cl^-):

$$\text{Anion gap} = (\text{measured cations}) - (\text{measured anions}) = ([Na^+]+[K^+]) - ([HCO_3^-]+[Cl^-])$$

where $[Na^+]$, $[K^+]$, $[HCO_3^-]$, and $[Cl^-]$ are the mmol/L concentrations of these ions in serum

The normal range depends on local reference values of the measured electrolytes, but 10–16 mmol/L is typical. In health, the 'gap' is explained primarily by albumin, which is negatively-charged at physiological

pH. Hypoalbuminaemia therefore confounds the interpretation of the anion gap. This may be mitigated by applying a correction[2]:

$$\text{Corrected anion gap} = AG_{obs} + (0.25 \times ([Alb]_{norm} - [Alb]_{obs})$$

where AG_{obs} is the observed anion gap in mmol/L
$[Alb]_{obs}$ is the measured albumin concentration in mg/L
$[Alb]_{norm}$ is the normal albumin concentration (pragmatically, the midpoint of the local reference range, e.g. 44 mg/L))

In evaluating a patient with metabolic acidosis, the anion gap may be helpful in delineating, crudely, its mechanistic basis:

- An **elevated anion gap** suggests accumulation of acid other than hydrogen chloride (HCl). The acid dissociates to H^+ (which, through buffering, causes $[HCO_3^-]$ to fall) and a negatively-charged conjugate base, for example, lactate or oxalate. The base constitutes an 'unmeasured anion', and increases the anion gap.
- A **normal anion gap** suggests losses of sodium bicarbonate relative to chloride, or a defect in renal excretion of HCl. Either way, the result is metabolic acidosis with hyperchloraemia. Since the fall in $[HCO_3^-]$ (either through losses or buffering) occurs in proportion to the rise in $[Cl^-]$, the anion gap remains normal.

Drug causes of metabolic acidosis

This review focuses on drugs that cause or exacerbate metabolic acidosis during therapeutic use (Table 1), rather than those which cause acidosis only in toxicity.

Normal anion gap (hyperchloraemic) metabolic acidosis

Intestinal fluid losses

The commonest cause of normal anion gap metabolic acidosis is sodium bicarbonate losses from the intestinal tract (distal to the stomach). This is usually evident from the clinical context. Where relevant, drug causes of diarrhoea, which are numerous, should be considered.

Renal tubular acidosis

Renal tubular acidosis (RTA) describes a group of conditions in which there is impairment of urinary HCl excretion in the distal tubule (type 1), HCO_3^- reabsorption in the proximal tubule (type 2), or hypoaldosteronism (type 4). All cause metabolic acidosis with a normal anion gap, assuming glomerular filtration is normal. Types 1 and 2 RTA usually cause severe acidosis with hypokalaemia, while type 4 RTA causes mild acidosis with hyperkalaemia.

Type 1 (distal) RTA

The antifungal drug **amphotericin** has various nephrotoxic effects, including causing dose-related impairment of urinary acidification with hypokalaemia.[3] This may be due to increased permeability of the tubular epithelium, permitting diffusion of ions along their concentration gradients (H^+ from filtrate into

tubular cells; K^+ from tubular cells into filtrate).[4] Liposomal amphotericin is less toxic to the glomerular epithelium than conventional amphotericin. However, the tubular epithelium remains sensitive to high-dose liposomal amphotericin,[5] so acidosis and hypokalaemia can still occur.[6]

Lithium, a mood stabilising agent, primarily affects renal concentrating capacity (causing nephrogenic diabetes insipidus), but it can also cause mild impairment of tubular acid secretion, giving an incomplete type 1 RTA picture.[7,8]

Type 2 (proximal) RTA

Type 2 RTA may occur as part of a syndrome of generalised proximal tubular dysfunction (Fanconi syndrome). Functions of the proximal tubule include recovering organic solutes, potassium and phosphate from filtrate, and excreting HCl. Accordingly, the features of Fanconi syndrome include glycosuria, aminoaciduria, proteinuria, hypokalaemia, hypophosphataemia and hyperchloraemic acidosis.

Ifosfamide, a cytotoxic alkylating agent, causes dose-related nephrotoxicity through proximal tubular injury, resulting in a Fanconi-like syndrome.[9] This effect is not shared by its structural relative cyclophosphamide. This may be because it is mediated by chloroacetaldehyde, which is a major metabolite of ifosfamide but only a minor metabolite of cyclophosphamide.[10] Other drug causes of Fanconi-like syndromes include the anticonvulsant **valproate** and the nucleotide reverse transcriptase inhibitor **tenofovir**.[11,12]

Acetazolamide, used mainly in glaucoma, causes isolated proximal RTA (i.e. without the other features of Fanconi syndrome) through inhibition of carbonic anhydrase. Indeed, on the rare occasions in which it is used as a respiratory stimulant, metabolic acidosis is a desired effect. The anticonvulsants **topiramate** and **zonisamide** can also inhibit carbonic anhydrase and cause isolated proximal RTA.[13,14] The risk appears not to be predictable from dosage or duration of therapy, and may be related to genetic susceptibility factors.[13]

Type 4 RTA (hypoaldosteronism)

Deficiency of aldosterone action, due to absolute or relative aldosterone deficiency, reduces sodium reabsorption in the collecting tubules. This lowers the electrochemical gradient that drives K^+ and H^+ excretion. In addition, it probably reduces tubular ammonium production and excretion elsewhere in the nephron.[14] The overall effect is mild metabolic acidosis with a normal anion gap and hyperkalaemia.

Drug causes of hypoaldosteronism include the aldosterone antagonists **spironolactone** and **eplerenone**.[15,16] **Trimethoprim** also has aldosterone-antagonist effects and has been associated with hyperkalaemic RTA.[17,18] Usually, though not always, this in the context of high-dose treatment with **co-trimoxazole**, of which trimethoprim is a constituent. The calcineurin inhibitors **ciclosporin** and **tacrolimus** can induce aldosterone resistance, resulting in type 4 RTA; they can also cause hypokalaemic (type 1 or 2) RTA and other forms of tubular dysfunction.[19]

Sodium chloride

Sodium chloride 0.9% is a widely used intravenous infusion solution. It causes a dose-dependent hyperchloraemic metabolic acidosis.[20] Hyperchloraemia results from the chloride concentration of the solution which, at 154 mmol/L, is substantially higher than that of serum (around 100 mmol/L). Acidosis

may be due to an unbalanced effect on the CO_2/HCO_3^- buffer system: HCO_3^- is diluted while PCO_2 is independently regulated by respiration.[21] An alternative explanation is through its effect on the strong ion difference (SID).[22] The SID is the difference between positively- and negatively-charged fully-dissociated ions [$(Na^+ + K^+ + Mg^+ + Ca^{2+}) - (Cl^- + lactate)$]), and is argued to be one of three independent variables that determine serum pH (the others being PCO_2 and total weak acid concentration).[23] Hyperchloraemia reduces the SID which, to maintain electroneutrality, causes $[H^+]$ to increase (so pH falls). Whether this mathematical explanation reflects the biochemical mechanisms is debated.[21,22]

'Balanced' crystalloid solutions, which have an electrolyte composition closer to that of serum (such as Hartmann's solution), cause less metabolic derangement than sodium chloride.[20] Metabolism of lactate contained in these solutions has an alkalinising effect.

Elevated anion gap metabolic acidosis

Renal failure

Impaired glomerular filtration leads to accumulation of non-volatile acids. These include inorganic acids (e.g. sulfuric and phosphoric acids) and non-metabolisable organic acids (uric, pyroglutamic and hippuric acids). The result is metabolic acidosis with an elevated anion gap. Nephrotoxic drugs, which are numerous, should always be considered as possible causes or contributors to impaired renal function.

Lactic acidosis

In anaerobic metabolism, lactate is produced from pyruvate to replete cellular stores of nicotinamide adenine dinucleotide (NAD^+), which is necessary to sustain continued glycolysis. Subject to sufficient oxygen, lactate is subsequently converted back to pyruvate, to be used in oxidative phosphorylation (aerobic respiration to generate adenosine triphosphate (ATP)) or gluconeogenesis (which requires ATP). The net effect on acid-base balance is neutral, as H^+ released during glycolysis is consumed during lactate metabolism. However, if oxidative phosphorylation is impaired, as in hypoxia, the unbalanced release of H^+ from glycolysis and ATP hydrolysis causes acidosis. As this occurs alongside lactate accumulation, the resulting syndrome may be termed 'lactic acidosis' (defined clinically as acidaemia with a serum lactate concentration >5 mmol/L). Mechanistically, however, it should be appreciated that lactate is not itself responsible for acidosis.[24]

Lactic acidosis associated with global tissue hypoxia (and the resulting shift from aerobic to anaerobic respiration) is termed 'type A'. Drugs that reduce cardiac output or tissue perfusion (e.g. negatively-inotropic and vasodilatory drugs, such as beta-blockers and nitrates, respectively) may contribute to this, although usually in the context of an acute illness or overdose. Lactic acidosis may also arise from accelerated aerobic glycolysis (i.e. without global tissue hypoxia; 'type B') due to β_2-adrenergic stimulation.[25] β_2-agonist drugs, including the bronchodilator salbutamol and the inotrope dopexamine, may cause lactic acidosis through this mechanism.

The nucleoside reverse transcriptase inhibitors stavudine and didanosine,[26] and the anti-staphylococcal antibiotic linezolid**,**[27] can cause type B lactic acidosis at therapeutic dosages by interfering with mitochondrial oxidative phosphorylation. Likewise, the anti-hyperglycaemic agent metformin**,** widely

used in type 2 diabetes, acts through inhibition of complex I of the electron transport chain,[28] impeding oxidative phosphorylation. In toxicity (overdose or reduced renal elimination), this may cause lactic acidosis. Whether metformin causes lactic acidosis during therapeutic use in patients with normal renal function has been a subject of much debate. Case reports notwithstanding, clinical trial and observational data suggest that the risk is not significantly higher than the background rate in patients with diabetes.[29]

A rare but serious adverse effect of the anaesthetic agent propofol is a syndrome characterised by metabolic acidosis, rhabdomyolysis, renal failure and cardiovascular collapse. This may be mediated by mitochondrial toxicity, either through interference with the electron transport chain (at complexes II and IV) or fatty-acid oxidation, causing failure of ATP production and metabolic acidosis with hyperlactataemia.[30] This 'propofol infusion syndrome' (PRIS) is probably related to cumulative exposure, and it is therefore recommended that the rate of prolonged infusions should not exceed 4 mg/kg/hr.[31] However, PRIS has been reported after short infusions,[30] suggesting susceptibility factors in some individuals.

Propylene glycol is used as a solvent in some parenteral drug preparations, notably lorazepam and diazepam. High-dose treatment with these agents may cause high anion gap metabolic acidosis associated with a high osmolal gap (the difference between measured and calculated serum osmolality).[32] Metabolism of propylene glycol produces varying amounts of L-lactate (the isomer that predominates in mammalian biology, and which measured in most clinical assays) and D-lactate. D-lactic acidosis should be suspected in patients with risk factors (including exposure to drugs containing propylene glycol as an excipient) and high anion gap acidosis, in whom the anion gap is not explained by the measured L-lactate concentration.

Ketoacidosis

Ketoacidosis is most commonly seen in states of absolute or near-absolute insulin deficiency (usually, but not exclusively, in type 1 diabetes), and in alcohol abuse. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors (dapagliflozin, canagliflozin, empagliflozin) have been associated with euglycaemic diabetic ketoacidosis.[33] The tendency to ketoacidosis is most likely to be related to the underlying insulin deficiency state. However, the contribution of SGLT-2 inhibitors complicates the picture, as hyperglycaemia (a key diagnostic clue) may be mild or absent due to drug-induced glycosuria. Furthermore, the resulting osmotic diuresis may exacerbate hypovolaemia.

Pyroglutamic acidosis

Pyroglutamic acidosis arises from disruption of the ATP-dependent γ-glutamyl cycle. The resulting accumulation of pyroglutamic acid (5-oxoproline) causes high anion gap metabolic acidosis. Although a rare cause of metabolic acidosis, it is important due to its association with two widely used drugs, paracetamol and flucloxacillin,[34,35] and because it is often unrecognised. Chronic paracetamol therapy contributes to the risk of pyroglutamic acidosis through depletion of glutathione stores, while flucloxacillin inhibits 5-oxoprolinase, the enzyme responsible for metabolising pyroglutamic acid to glutamic acid.

Pyroglutamic acidosis should be suspected in cases of high anion gap acidosis where the anion gap cannot be attributed to lactate or ketone accumulation, particularly if there are other risk factors (e.g. malnutrition, paracetamol and flucloxacillin therapy). The diagnosis may be confirmed by urinary organic acid measurement, although this is likely to be retrospective. Management is centred on supportive care, stopping causative/contributory agents, and replenishing glutathione stores with acetylcysteine.[34,35]

Conclusion

Many drugs can contribute to metabolic acidosis, acting through diverse mechanisms. A careful drug history should always form part of the assessment of a patient with metabolic acidosis. This should be evaluated alongside the clinical features, serum acid-base status, anion gap (corrected for hypoalbuminaemia where applicable) and associated biochemical abnormalities, in order to delineate its cause and determine best management.

Clinicopathological classification	Drug causes	Comments
Normal anion gap		
Intestinal fluid losses	Drug causes of diarrhoea	Intestinal fluid loss (distal to the stomach), including from drug-induced diarrhoea, causes sodium bicarbonate losses.
Type 1 RTA	Amphotericin	Associated with hypokalaemia. Amphotericin is also toxic to glomerular epithelium, impairing filtration; the liposomal formulation is less glomerulotoxic.
	Lithium	Also causes nephrogenic diabetes insipidus.
Type 2 RTA		
Isolated acidosis and hypokalaemia	Acetazolamide Topiramate Zonisamide	Mediated by inhibition of carbonic anhydrase.
With other features of proximal tubular dysfunction (Fanconi syndrome)	Ifosfamide Valproate Tenofovir	Associated features may include glycosuria, aminoaciduria, proteinuria, hypokalaemia, and hypophosphataemia.
Type 4 RTA (hypoaldosteronism)	Spironolactone Eplerenone Trimethoprim Ciclosporin Tacrolimus	In type 4 RTA the acidosis is usually mild and associated with hyperkalaemia.
Sodium chloride infusion	0.9% sodium chloride	Dose-related hyperchloraemic acidosis, associated with a reduction in the strong ion difference.
Elevated anion gap		
Nephrotoxicity	Nephrotoxic drugs (numerous)	Due to accumulation of various inorganic and non-metabolisable organic acids.
Lactic acidosis		
With global tissue hypoxia ('type A')	Negatively inotropic and vasodilatory drugs	Unlikely as a cause of lactic acidosis during chronic stable therapy, but if combined with an acute process (e.g. sepsis), drugs that reduce cardiac output (e.g. β-adrenergic blockers) may exacerbate tissue hypoxia and worsen lactic acidosis.
Without global tissue hypoxia ('type B')	Salbutamol Dopexamine	Accelerated aerobic glycolysis driven by β_2-adrenergic stimulation.
	Stavudine Didanosine Linezolid	Interference with mitochondrial function.
	Propofol	Mitochondrial toxicity. Usually, but not exclusively, related to extended/high-dose infusion. Other features of the 'propofol infusion syndrome' include renal failure, cardiovascular collapse, rhabdomyolysis and hyperlipidaemia.
	Metformin	A commonly cited example of drug-induced lactic acidosis, but metformin probably does not significantly increase the risk at therapeutic dosage.
D-lactic acidosis	Lorazepam and diazepam (IV preparations)	Caused not by the drug, but the excipient propylene glycol. Associated with high osmolal gap. Routine clinical assays may not detect D-lactate.
Euglycaemic diabetic ketoacidosis (DKA)	Dapagliflozin Canagliflozin Empagliflozin	DKA is caused by the underlying insulin deficiency state (usually type 1 diabetes), but the SGLT-2 inhibitors complicate the picture by preventing or minimising hyperglycaemia.
Pyroglutamic acidosis	Paracetamol	Depletes glutathione reserves.
	Flucloxacillin	Inhibits 5-oxoprolinase.

Table 1. Drug causes of metabolic acidosis.

RTA, renal tubular acidosis; SGLT-2, sodium-glucose co-transporter 2; IV, intravenous.

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