Drug Induced High Anion-Gap Metabolic Acidosis Presenting with Shortness of Breath: A Case Report

Maheshi Wijayabandara¹, Champika Gamakaranage²*, and Saroj Jayasinghè³

¹Registrar in Geriatric Medicine, University Medical Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka
²Consultant Physician and Senior Lecturer in Medicine, Department of Clinical Medicine, University of Colombo, Sri Lanka
³Chair Professor, Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Sri Lanka

*Corresponding Author: Champika Gamakaranage, Consultant Physician and Senior Lecturer in Medicine, Department of Clinical Medicine, University of Colombo, Sri Lanka.

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Abstract

Introduction: High anion gap metabolic acidosis can occur due to various medications. This case report presents a patient with high anion gap metabolic acidosis due to azithromycin and paracetamol combination presenting with shortness of breath.

Case Presentation: A 19-year-old Sri Lankan girl who was being evaluated for nephrotic syndrome presented with shortness of breath for two days. Three days prior to the current presentation she was administered a cumulative dose of azithromycin 1 gram and paracetamol (acetaminophen) 4 grams over two days for an upper respiratory tract infection. On examination she was having tachypnea with 100% saturation on room air. Rest of the examination did not reveal a positive finding. Her arterial blood gas analysis showed a high anion gap metabolic acidosis with respiratory compensation. Ketoacidosis, lactic acidosis, acute kidney injury and deliberate overdose of toxic compounds were excluded. Azithromycin and paracetamol were discontinued. Her metabolic acidosis was completely recovered over two days, only with supportive care.

Conclusion: Azithromycin and paracetamol combination could be a rare cause for high anion gap metabolic acidosis. High index of suspicious is necessary to prompt detection and discontinuation of culprit medicines.

Keywords: High Anion Gap Metabolic Acidosis; Azithromycin; Paracetamol; Sri Lanka

Abbreviations

HAGMA: High Anion Gap Metabolic Acidosis; AG: Anion Gap

Introduction

High Anion Gap Metabolic Acidosis (HAGMA) has a number of varied causes. Drug induced HAGMA is an uncommon encounter but needs good awareness among clinicians. There are multiple drugs known to cause HAGMA. This case report presented HAGMA due to azithromycin and/or paracetamol presenting with shortness of breath.

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Anion gap (AG) in serum is calculated using routinely measured serum sodium (Na), serum potassium (K), serum chloride (Cl) and serum bicarbonate (HCO₃) values as follows (all expressed in mmol/L) [1]:

\[
AG = Na + K - (Cl + HCO₃)
\]

The reference range for normal AG is 3 - 11 mmol/L. The AG is the difference between the measured cations (Na and K) and measured anions (Cl and HCO₃) which represent the amount of unmeasured anions. These include sulphates (SO₄), phosphates (PO₄) and proteins in the serum. When the anion gap is elevated (i.e. when it is > 11 mmol/L) it is due to the presence of additional anions in the serum.

Severe volume depletion (hyperalbuminemia), metabolic or respiratory alkalosis, hyperphosphatemia, paraproteinemia and metabolic acidosis are amongst the causes of high anion gap.

Causes of high anion gap metabolic acidosis are ketoacidosis (e.g. diabetes, alcohol, and starvation), lactic acidosis, methanol or ethylene glycol intoxication, toluene poisoning, some drugs and chronic kidney disease [1]. Drugs causing HAGMA includes aspirin, isoniazid, paracetamol, iron, theophylline and aminoglycosides. Azithromycin is a rare cause of HAGMA. This case report presents a patient with HAGMA due to Azithromycin/Paracetamol who improved after discontinuation of the culprit medicines and supportive care.

Case Presentation

A 19-year-old Sri Lankan girl who was being evaluated for nephrotic syndrome for three months presented with a two-day history of progressive shortness of breath. Her baseline serum creatinine was 50 µmol/L and there was no reduction of urine output. Three days prior to the current presentation she had headache, cold and sore-throat. She did not complain of fever, cough, chest pain, calf swelling or abdominal swelling. She did not consume alcohol.

She was prescribed azithromycin 500 mg daily and paracetamol 1g 8-hourly by a general practitioner. She had taken two doses of azithromycin and four doses of paracetamol before the presentation. Apart from the above medications she was only on atorvastatin 10 mg once at night for dyslipidaemia due to nephrotic syndrome. On examination her body mass index was 24 kg/m². She was not pale, afebrile, pulse rate was 76 beats per minute, blood pressure was 120/80 mmHg, heart sounds were normal, saturation on room air was 100%, respiratory examination was normal except for the respiratory rate of 36 per minute. There was no evidence of deep vein thrombosis. Throat and ear examinations were normal. Abdomen was soft and non-tender, without evidence of ascites.

A summary of her biochemical parameters are shown in table 1. On admission her arterial blood gas analysis showed a compensatory metabolic acidosis with a high anion gap of 34. Azithromycin and paracetamol were discontinued and subsequently her metabolic acidosis was corrected over two days, only with supportive care as depicted in the table 2. Her nephrotic syndrome was later diagnosed as mesangio proliferative glomerulonephritis with a renal biopsy.

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary blood sugar (mg/dL)</td>
<td>113</td>
<td>(&lt; 2)</td>
</tr>
<tr>
<td>Serum lactate (mmol/L)</td>
<td>1.0</td>
<td>(&lt; 2)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>45</td>
<td>(60 - 110)</td>
</tr>
<tr>
<td>Blood urea (mmol/L)</td>
<td>4.1</td>
<td>(2.5 - 7.1)</td>
</tr>
<tr>
<td>Urine for ketone bodies (mg/dL)</td>
<td>Not detected</td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>36</td>
<td>(35 - 55)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>28</td>
<td>(10 - 40)</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>31</td>
<td>(7 - 56)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>&lt; 6</td>
<td>&lt; 6</td>
</tr>
</tbody>
</table>

*Table 1: Biochemical parameters of the patient.*

Parameter | On admission-Day 0 | Day-1 | Day-2 | Day-3
---|---|---|---|---
pH | 7.39 | 7.41 | 7.41 | 7.42
PaCO₂ (mmHg) | 21.6 | 22.1 | 29.9 | 36.1
HCO₃ (mmol/L) | 12 | 15.2 | 19.5 | 22.1
Sodium (mmol/L) | 138 | 137 | 140 | 141
Potassium (mmol/L) | 4 | 3.9 | 3.8 | 4
Chloride (mmol/L) | 96 | 108 | 110 | 110
Anion gap | 34 | 17.7 | 14.3 | 12.9

Table 2: Progression of the results of the arterial blood gas analysis.

Discussion

Presented in this case report is a patient with HAGMA caused by azithromycin and paracetamol combination who improved following the discontinuation of culprit medicines. Initial clinical presentation of worsening shortness of breath was due to HAGMA causing respiratory compensation. There were no clinical features of pneumonia, pulmonary embolism or cardiac failure to explain her shortness of breath. The common causes for HAGMA such as acute kidney injury, ketoacidosis, lactic acidosis or overdose of methanol, ethylene glycol or deliberate overdose of medicines were excluded by the history and biochemical evaluation. She had symptoms of an upper respiratory tract infection and was treated by a general practitioner with azithromycin and paracetamol. When she presented to us she was administered a cumulative dose of azithromycin 1 gram and paracetamol (acetaminophen) 4 grams over two days.

Acute overdose of paracetamol produces a HAGMA due to its’ hepatotoxicity leading into lactic acidosis and acute kidney injury [2]. However, our patient was administered only 4 grams of paracetamol over two days. Chronic administration of paracetamol is associated with HAGMA due to transient 5-oxoprolinuria caused by reduced plasma glutathione levels [3]. Malnutrition, chronic alcohol abuse, pregnancy, diabetes mellitus, sepsis, liver and renal impairment are some of the risk factors which predispose to transient 5-oxoprolinuria associated with chronic administration of paracetamol [3,4]. Our patient did not possess any of the risk factors nor history of chronic administration of paracetamol.

Concomitant use of flucloxacillin and paracetamol in the background of sepsis causing HAGMA due to 5-oxoprolinuria is reported in the literature [5]. Flucloxacillin inhibits 5-oxoprolinase which converts 5-oxoproline to L-glutamate [5]. Ciprofloxacin and netilmicin also inhibits 5-oxoprolinase resulting in 5-oxoprolinuria [5,6]. However, azithromycin is not well recognized to cause HAGMA.

Because of the resource limited setting in Sri Lanka, urinary level of 5-oxoproline of our patient could not be measured.

In our patient the most possible cause for HAGMA was concluded as the co-administration of azithromycin and paracetamol. After discontinuation of the offending medicines her acidosis completely recovered only with supportive care. The exact mechanism of acidosis produced by azithromycin and paracetamol is not known and needs more research.

Conclusion

High index of suspicion is necessary to detect HAGMA caused by medications administered at therapeutic doses. Azithromycin and paracetamol combination can cause HAGMA even in the absence of traditional risk factors.

Conflict of Interest

None.

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Consent and Ethical Background
Written informed consent was obtained from the patient for publication of this case report.

Authors’ Contributions
MW and CG contributed equally to the patient’s care. MW wrote the initial case report. CG and MW both contributed to the literature survey and case analysis. Both authors read and approved the final manuscript. SJ contributed in discussion and analysis of case.

Bibliography

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