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Acute Haemolysis In A Glucose-6-Phosphate-Dehydrogenase Deficient Patient Receiving High-dose Vitamin C Therapy For Metastatic Colorectal Cancer: A Case Report

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Introduction

The use of intravenous high-dose ascorbic acid (vitamin C) in cancer remains an area of contention. It is occasionally used as an adjunct to chemotherapy by physicians and in naturopathic settings.

Evidence for its use is inconclusive with some papers reporting it has the potential to target cancer cell vulnerabilities, slow cancer growth, improve survival and reduce chemotherapy toxicity. Despite a lack of definitive evidence, it has a favourable safety profile and potential anti-tumour effects, therefore continues to be used off-license. The effects of high-dose ascorbic acid are being trialed in a variety of conditions including sepsis, rheumatoid arthritis, pneumonia and tetanus, therefore the conclusions from this case report are applicable to a population wider than solely cancer patients.

We present a case of life-threatening haemolysis caused by high-dose vitamin C administration in the context of glucose-6-phosphate-dehydrogenase (G6PD) deficiency that disputes the safety of this therapy for particular patients.

Table 1: Blood results

Blood test	Result on admission	Result 3 weeks previously	Units	Normal range
Haemoglobin	49	118	g/L	130-170
White Cell Count	28	12	x10^9/L	3-10
Platelets	671	401	x10^9/L	150-400
Bilirubin	151	12	umol/L	0-20
Conjugated Bilirubin	84	-	umol/L	0-5
Alanine Transaminase	44	47	IU/L	10-50
Alkaline phosphatase	381	436	IU/L	40-129
Creatinine	73	73	umol/L	66-112
C-reactive protein	153	137	mg/L	0-4
Reticulocytes (abs)	201.8	-	x10^9/L	16.7-112
DAT	negative	-	-	-
Haptoglobin	<0.1	-	g/L	0.3-2.0
Methaemoglobin	1.9	-	%	0-1.5
Lactate Dehydrogenase	1334	-	IU/L	135-225
Carboxyhaemoglobin	7.2	-	%	0-2
Lactate	2.8	-	mmol/L	0.6-2.4
PH	7.37	-	-	7.35-7.45

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Case Report

A male patient in his 5th decade presented with a two-day history of light-headedness, dyspnoea, dark urine, and yellow discolouration of the skin. Relevant past medical history included a diagnosis of caecal cancer with lung and liver metastasis. Having declined palliative chemotherapy with FOLFOXIRI, he had sought an alternative treatment in the private sector, high-dose Vitamin C. Prior to administration the patient underwent G6PD screening which suggested a mild deficiency, however the decision was made to continue with treatment. The aforementioned symptoms had begun within a few hours of administration of the Vitamin C infusion.

Examination revealed obvious ictera, a non-tender hepatomegaly with clear chest on auscultation. Per-rectum examination was negative for melaena. He was tachycardic and hypoxic, requiring 15 litres of oxygen to maintain appropriate saturations.

Initial investigations revealed a significant anaemia, with haemoglobin 49g/L (118g/L three weeks prior to admission), and a hyperbilirubinemia (see table 1).

Haemolysis screen was positive with markedly elevated reticulocytes, low haptoglobin and subsequent blood film was reported as polychromasia, spherocytes and occasional red blood cells in keeping with haemolysis. G6PD screen on admission was interestingly negative.

He was transfused four units of red blood cells with good increment in his haemoglobin and resolution of his hyperbilirubinemia. He was discharged 3 days later.

Discussion

There is a growing body of evidence to suggest haemolysis can be induced by high-dose ascorbic acid. A number of case reports have displayed the link between administration of high-dose ascorbic acid and the development of haemolysis in patients with a background of G6PD deficiency, this is the first of those that occurred in the context of cancer treatment.

G6PD deficiency is a common inherited X-linked recessive disorder and is seen mostly in malaria-prevalent populations for example Asia and the Mediterranean. Ordinarily, the enzyme G6PD protects cells including erythrocytes from oxidative stress. In G6PD deficient populations, precipitants including medications, food and infections can all trigger haemolytic anaemia.

In vitro studies have shown the varying effects of ascorbate are dose-dependent. At low doses, ascorbic acid is a powerful anti-oxidant. However, high doses of ascorbic acid are thought to promote hydrogen peroxide production which depletes already limited glutathione supplies (an anti-oxidant) precipitating damage and haemolysis of G6PD-deficient erythrocytes (see image 1).

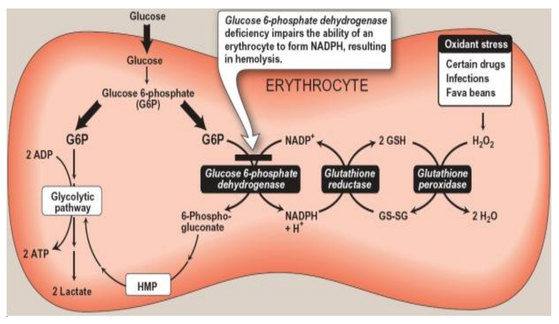

Image 1: G6PD pathway. Source: https://www.studyblue.com

Amongst the usual biochemical markers of haemolysis including hyperbilirubinaemia, reduced haptoglobins, an ABG can quickly indicate a haemolytic process. Heme capatoblism results in both raised carboxyhaemoglobin (from raised carbon monoxide production), and methaemoglobin.

As in this case, during acute haemolysis, G6PD assays can be falsely negative as both the degradation of erythrocytes with low G6PD levels and subsequent reticulocytosis of erythrocytes with preserved levels of G6PD, can lead to normal levels of G6PD[3].

Conclusively, this case highlights the need for reconsideration of the safety of high dose vitamin C therapy in this population and suggests the requirement for G6PD deficiency screen prior to administration. Currently high-dose ascorbic acid is used off-licence and considered a relatively benign therapy, this is a reminder like all other medications ascorbic acid at supraphysiological levels has the potential to cause serious side effects.

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