CASE REPORT

Intra-operative acidosis during 5-aminolevulinic acid assisted glioma resection

Ian Anderson,¹ Thomas Naylor,¹ Justin McKinlay,² Gnanamurthy Sivakumar¹¹Department of Neurosurgery, Leeds General Infirmary, Leeds, West Yorkshire, UK²Department of Anaesthetics, Leeds General Infirmary, Leeds, West Yorkshire, UK

Correspondence to

Ian Anderson,
ian.anderson4@nhs.net

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SUMMARY

A 47-year-old man underwent 5-aminolevulinic acid assisted resection of high grade glioma. Intraoperatively, he developed a compensated lactic acidosis that was managed medically and did not cause long term complications.

BACKGROUND

5-aminolevulinic acid (5-ALA) is becoming increasingly commonly employed during glioma resection, in order to increase the extent of resection for patients with high grade glioma. As more patients receive this treatment, it is important that clinicians are made aware of the potential complications and side effects of this treatment, such that any metabolic abnormality can be identified early and corrected appropriately. Similarly, this case should be borne in mind, in conjunction with review of patients' other comorbidities prior to planning a 5-ALA-guided operation.

CASE PRESENTATION

A 47-year-old man presented with a 1-month history of gradual onset, worsening headaches. The headaches were noted to increase in severity on coughing and sneezing. There were no other neurological symptoms reported. He had no medical history and was not on any regular medication. He has no known drug allergies.

On neurological examination, the patient was noted to have very mild left upper limb weakness only. Tone, reflexes and sensation were normal in all four limbs. There was no cranial nerve deficit. Fundoscopic examination demonstrated bilateral papilloedema.

INVESTIGATIONS

A contrast-enhanced CT head was performed, which demonstrated a solitary, 6.5 cm right frontal lobe ring enhancing mass, which was felt likely to represent a primary, high-grade brain tumour.

A subsequent MRI confirmed a 7.5×4.5 cm largely necrotic, peripherally enhancing irregular mass in the right frontal lobe. The cystic portion did not demonstrate evidence of restricted diffusion. A considerable amount of surrounding oedema was noted (figure 1).

DIFFERENTIAL DIAGNOSIS

The working differential diagnosis was that of a high grade, primary intrinsic brain tumour.

TREATMENT

The case was discussed in the neurology/oncology multidisciplinary team meeting and the decision was agreed that the patient would be a suitable candidate for debulking surgery.

Oral 5-ALA (Gliolan), 1500 mg (20 mg/kg dose; patient weight 74.8 kg), was administered orally prior to surgery, without immediate complication. Induction of general anaesthetic was at 3 h and 10 min after administration.

The surgery itself was straightforward and without particular complication. The tumour displayed an appropriate level of fluorescence and the uptake was increased as compared with the surrounding tissue.

During the course of the surgery, the patient's arterial blood gases demonstrated a progressive compensated lactic acidosis (table 1).

OUTCOME AND FOLLOW-UP

The patient's blood results normalised and when next reviewed at 24 h postsurgery, full blood count, and urea, electrolyte and liver function tests were all found to be within normal limits, although subsequent arterial blood gases were not performed. No further action or investigation has been required and the patient had an uncomplicated postoperative course.

DISCUSSION

5-ALA as a cause of lactic acidosis

The use of 5-ALA as a means of increasing the extent of malignant tumour resection has grown in popularity during the start of the 21st century, having been shown to increase rates of complete resection of contrast-enhancing malignant glioma from 36% to 65%.¹ It is also one of the most researched fluorescence-inducing compounds and has been the subject of various trials to assess its efficacy and safety.

5-ALA is a biochemical precursor found naturally in cells as part of the porphyrin and haem synthesis pathways.² Administration of excess levels of the compound results in the accumulation of endogenous fluorescent and photosensitising porphyrins, in particular protoporphyrin IX (Pp-IX).²⁻³ Pp-IX uptake is almost undetectable in healthy brain tissue but readily accumulates in malignant glioma tissues, possibly due to poor blood-brain barrier penetration in the healthy brain or higher uptake of 5-ALA by neuroectodermal tumour tissues.¹⁻²⁻⁴ This disparity in uptake effectively highlights tumour tissue margins as fluorescent when viewed under blue-light.

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Figure 1 (MRI sequences shown are, clockwise from top left: T1 with gadolinium, T2, ADC map, DWI images) Subsequent MRI imaging showing a large, cystic tumour with no evidence of restricted diffusion seen. Radiologically, this was felt most likely to represent a high grade glioma. ADC, Apparent diffusion coefficient; DWI, Diffusion weighted imaging.

A thorough search of the literature failed to uncover any previous documentation of intraoperative lactic acidosis as a side effect of 5-ALA administration. The general consensus is that

5-ALA is very well tolerated with very minimal, if any, side effects experienced by most patients. Documented possible adverse reactions attributed to 5-ALA administration include

Table 1 Perioperative arterial blood gas results

Time	3:55	5:06	5:13	5:37	6:42	9:46	10:30
Post 5-ALA (h:min)	Samples taken during operation (patient intubated, ventilated and sedated)				Samples taken in recovery (patient extubated)		
pH	7.416	7.375	7.379	7.370	7.410	7.374	7.37
pCO ₂ (kPa)	4.81	5.28	5.09	5.01	4.20	4.12	3.95
pO ₂ (kPa)	30.84	26.12	27.25	27.11	28.20	21.69	21.75
HCO ₃ (mmol/L)	23.3	22.6	22.2	21.6	20.9	19.1	18.5
BE (mmol/L)	-1.4	-2.3	-2.8	-3.5	-4.3	-6.6	-7.4
Na ⁺ (mmol/L)	135.9	137.2	137.4	138.6	137.4	138.6	140.2
K ⁺ (mmol/L)	4.62	4.90	4.84	4.71	4.91	4.72	4.27
Ca ²⁺ (mmol/L)	1.09	1.05	1.04	1.06	1.01	1.01	0.98
Cl ⁻ (mmol/L)	104	104	105	107	108	110	112
Glu (mmol/L)	7.1	6.8	6.6	6.3	6.9	6.2	6.1
Lac (mmol/L)	4.34	5.07	5.04	5.13	5.61	6.20	6.54

5-ALA, 5-aminolevulinic acid.

vomiting and nausea, mild liver enzyme elevation, mild photosensitivity and hypotension. These side effects were experienced more frequently following much higher doses of 5-ALA than were used in our case, 30–60 vs <20 mg/kg.^{1 5–7} There are, however, previous reports of 5-ALA being responsible for a transient rise in lactate levels.^{8 9}

It could be assumed that either 5-ALA or Pp-IX causes side effects by inducing a porphyria-like state in the patient. Acute porphyrias, due to the accumulation of porphyrin metabolites, are associated with a range of symptoms including abdominal pain and gastrointestinal upset, vomiting, peripheral neuropathy, motor weakness, autonomic effects such as palpitations and increases in catecholamines, as well as electrolyte abnormalities. Acidosis is not an associated complication of acute porphyria and blood gas analysis has no role in the diagnosis of an acute attack. With the exception of occasional nausea and vomiting, previous research into the adverse effects of 5-ALA has failed to demonstrate any occurrence of other symptoms associated with porphyrias following administration, even at much higher doses than that which our patient received.^{3 5} The lack of evidence supporting a clinical connection between 5-ALA, a porphyria-like state and acidosis, appears to nullify this hypothesis. Given the timing of the rise in lactate levels, at over 10 h post-5-ALA administration, and the short plasma half-life of 5-ALA of 50 min, a direct connection with concentrations of the compound and lactate production is less likely than with concentrations of Pp-IX, which has been shown to peak at approximately 7 h post-5-ALA administration.^{10 11}

5-ALA and mitochondrial dysfunction

Previous studies of acute intermittent porphyria have demonstrated that chronic accumulation of 5-ALA and porphyrin metabolites has a direct effect on the mitochondria in which they are metabolised, which could be responsible for the lactic acidosis observed in our patient. It has been shown *in vitro* that elevated levels of 5-ALA auto-oxidise to create reactive oxygen species and cause mitochondrial DNA damage in a dose dependent manner.^{12–16} It is hypothesised that the damage to mitochondrial DNA results in transient dysfunction of metabolic processes, including impairment of aerobic uptake of pyruvate, leading to an increase in lactate production.^{8 9} One retrospective assessment of lactate levels following the preoperative use of 5-ALA for resection of glioma demonstrated elevated levels immediately post-operation of 2.7 ± 0.7 mmol/L compared to 2.1 ± 0.9 in the non-5-ALA group. In both groups, lactate levels settled to normal by day 1 postoperation.⁸ Another report brings to attention a case with some resemblance to ours, in which postinduction lactate was measured at 3.4 mmol/L, peaked at 4.7 mmol/L and persisted throughout the operation until returning to normal levels approximately 36 h postinduction.⁹ It was noted in that case that the hyperlactataemia was isolated without any physiological changes in overall acid–base status and with no evidence of acidaemia, and the authors concluded that there had been no short term harm suffered as a consequence. It is possible that our case represents a similar but more severe reaction to this.

The photosensitive nature of Pp-IX, which allows it to be used in photodynamic therapies in topical applications, may also have caused mitochondrial damage, impacting on acid–base balance and lactate production. Through photic stimulation, Pp-IX forms cytotoxic 5-ALAPDT.

This chemical is known to cause irreversible intracellular photochemical and biological changes resulting in mitochondrial apoptosis, which could theoretically increase lactate production

due to mitochondrial dysfunction.² With regard to side effects of 5-ALA due to its photosensitive properties, previous records comment only on occasional ‘sunburn’ and erythema caused by direct exposure to intense light, either operatively or in a window of 24–48 h postoperatively, and not an increase in lactate.^{4 16} It should also be noted that photodynamic therapy uses much more intense light exposure and for a more prolonged period of time than would occur as an excitation dose during tumour visualisation. Additionally, trials into the use of photodynamic therapy for glioma using 5-ALA have only ever identified transient cerebral oedema as a direct adverse reaction.¹⁷

Other possible causes

Given the absence of reports of lactic acidosis as a side effect of 5-ALA, other possible causes should be discussed. Blood pressure under anaesthesia was maintained within tight limits, as is usual during a neurosurgical procedure. This was accomplished with fluid loading, as opposed to vasoconstrictor use, which might have caused a rise in lactate levels. Repeated fluid boluses made no impact on the lactate concentration. Mixed central venous blood gas saturation (ScvO₂) was additionally checked, via a pre-placed central venous catheter. This was in excess of 80% saturation. The normal ScvO₂ value of 65% reflects an oxygen extraction of approximately 35%. ScvO₂ values <65% imply impaired tissue oxygenation, while the high value in this case would tend to reflect the increased inspired oxygen concentration used under anaesthesia, a high cardiac output (from optimised fluid loading) and reduced oxygen extraction from muscular paralysis but possibly mitochondrial disease.

Propofol infusion syndrome is well documented and presents with a profound metabolic acidosis, myocardial dysfunction, rhabdomyolysis and even death. However, all previously reported cases of propofol infusion syndrome occurred in critically ill patients being administered prolonged, high doses of propofol in conjunction with many other medications.

There are a small number of case reports of propofol triggered metabolic acidosis while being used as a sole short-term anaesthetic agent. These reports involve patients receiving continuous propofol anaesthesia for a variety of procedures (excision of olfactory bulb meningioma, cardiac ablation for AF, laparoscopic radical prostatectomy) who developed a profound lactic acidosis for which no other causative factor could be identified, all of which resolved once propofol infusion had been terminated.^{18–20} It is a possibility that our patient could have been affected by propofol, but it should be noted that in all three of the aforementioned cases, lactate and pH levels were normal well into the operation, with abnormalities only developing from 3 to 4 h postinduction. As shown in [table 1](#), lactate levels were already elevated and increasing within 1 h of induction in our case. It is interesting to note that a proposed mechanism for the propofol-induced acidosis is inhibition of mitochondrial respiration,¹⁸ and it has also been suggested that these cases may represent the reaction of a previously undiagnosed mitochondrial disorder to the oxidative stresses of propofol.²¹

While under anaesthesia, PaCO₂ levels were controlled to within normal limits (approximately 5 kPa). This is an important component of anaesthesia for intracranial surgery, as CO₂ levels will influence brain volume at the time of surgery. PaCO₂ levels that are too high will cause the brain to swell, necessitating excess retraction (and hence morbidity), and PaCO₂ levels that are too low result in excessive cerebral vasoconstriction, and introduce the possibility of ischaemia. Hence, during the anaesthetic phase, any respiratory compensation for the rise in lactate

did not occur, which is why the pH drifted downwards. Once controlled ventilation ceased, and the patient awoke, he then developed a fully compensated metabolic lactic acidosis, with PaCO₂ levels falling below normal (lowest value 3.95 kPa at 10 h posts ALA loading, coinciding with the highest recorded lactate level).

In spite of previous reports of propofol-induced metabolic acidosis, oral 5-ALA administration and its effect on mitochondrial function and respiration should still be considered as a possible cause of elevated lactate levels observed in the case discussed in this report. If there are case reports emerging of 5-ALA administration inducing lactic acidosis, then avoidance of total intravenous anaesthesia with propofol perhaps should be a recommendation until further research has delineated whether there is a true risk with this combination.

Learning points

- ▶ We observed a case of acidosis during 5-aminolevulinic acid (5-ALA) assisted brain surgery.
- ▶ While this acidosis proved transient in our case, clinicians should remain mindful of this potential side effect.
- ▶ Despite the above, 5-ALA would seem to be a safe adjunct to neurosurgical debulking of high-grade gliomas.
- ▶ Avoid propofol target controlled infusion where 5-ALA has been used, both intraoperatively and on intensive care afterwards.

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