



Posaconazole and isavuconazole induced hypomagnesaemia

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ARTICLE INFO

Keywords:

Mucormycosis

Posaconazole

Isavuconazole

Azole

Magnesium

1. Introduction

Mucormycosis is a relatively rare infection caused by ubiquitous fungi of the phylum Zygomycota, of which *Rhizopus arrhizus* is the most commonly isolated pathogen [1,2]. It has an extremely high mortality rate which varies with the degree of immunosuppression but remains over 50% for rhino-orbital-cerebral disease [1,2].

The recommended first line anti-fungal treatment is liposomal amphotericin B, however nephrotoxicity often limits its use and posaconazole is recommended as salvage therapy [3]. A novel agent isavuconazole is a triazole that has been used as salvage treatment for mucormycosis and is reported to have predictable pharmacokinetics and few drug interactions [4].

2. Case

A 73 year old man was admitted (Day 0) with left periorbital pain and paraesthesia. He had a past medical history of stable ischaemic heart disease and treated hypertension but no known diabetes mellitus. He had been previously treated as an outpatient with oral antibiotics for a presumed lower respiratory tract infection and a tapering dose of oral prednisone. He was admitted and treated with antibiotics (ceftriaxone, clindamycin and doxycycline) for presumed orbital cellulitis (Day 0–5). CT scan demonstrated widespread mucosal thickening of the left maxillary sinus and subsequent functional endoscopic sinus surgery (FESS) revealed extensive mucosal necrosis affecting the left inferior and middle turbinates, left lateral nasal wall, ethmoid bulla and middle meatus.

After developing sudden monocular proptosis and loss of vision on

day 6, liposomal amphotericin B (10 mg/kg) was commenced and he was urgently transferred to a referral centre for orbital exenteration (Day 7). Operative samples yielded a fungus which was identified morphologically as *Rhizopus arrhizus* (formerly *Rhizopus oryzae*). DNA sequence analysis of the internal transcribed spacer 1 (ITS1), 5.8S and ITS2 regions of the ribosomal DNA gene cluster confirmed the identification using published primers and standard sequencing methodologies [5]. The sequence showed 100% identity to the closest GenBank sequence [Accession AB097330]. The isolate had minimal inhibitory concentrations of 1 microgram/mL for amphotericin B and 0.25 microgram/mL for posaconazole.

On day 7, the haemoglobin A1C was determined to be 12.5% (113 mmol/mol) consistent with undiagnosed diabetes mellitus. On Day 9, he developed an acute kidney injury with a rise in creatinine to 165 micromol/L and the amphotericin was changed to intravenous posaconazole – combined initially with caspofungin – with therapeutic drug monitoring (TDM) demonstrating therapeutic blood levels. He underwent multiple debridements and improved with good glycaemic control.

On day 15, he developed severe symptomatic hypomagnesaemia (0.49 mmol/L) which was associated with generalised weakness and malaise. Over the next few months he required multiple admissions for intravenous magnesium replacement and, as other causes were excluded, we attributed this to the posaconazole. Despite oral supplementation of 4.5 g per day of magnesium aspartate away from meals and in the absence of diarrhoea, his serum concentration was unable to be maintained above 0.5 mmol/L without intravenous supplementation.

Over the next few weeks, other contributory factors for

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<https://doi.org/10.1016/j.mmcr.2018.09.007>

Received 23 June 2018; Received in revised form 16 August 2018; Accepted 20 September 2018

Available online 28 September 2018

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hypomagnesemia were addressed including the cessation of irbesartan, metformin, ondansetron, escitalopram and ranitidine. Other concomitant medications included amlodipine, aspirin, tapentadol, glimepiride, metoclopramide, rosuvastatin and oxycodone.

On day 149, posaconazole was changed to isavuconazole; however this was not tolerated due to development of nausea, vomiting, myalgia and lethargy. As the hypomagnesaemia persisted, despite intravenous and oral supplementation, the isavuconazole was ceased on day 166. He resumed posaconazole, with complete resolution of nausea, vomiting and myalgia, and remained on 4.5 g of oral magnesium aspartate to maintain normal serum magnesium levels. Progress imaging did not show any residual lesions, and he completed 14 months of treatment. Within two weeks of ceasing posaconazole, the serum magnesium returned to the normal range, without any oral supplementation.

3. Discussion

Given the increasing recognition and emergence of this disease, this case highlights a number of issues of which physicians should be aware including: the importance of appropriate use of antimicrobials and glucocorticoids; appropriate management of invasive mould infections with debridement where possible and, antifungal therapy supported by TDM; good glycaemic control; and the potential adverse effects of newer antifungal agents. We speculate that this otherwise immunocompetent patient developed mucormycosis in the context of impaired glucose tolerance which was triggered by steroid use. Both hyperglycaemia and glucocorticoid use represent well-established risk factors for mucormycosis, probably due to impaired chemotaxis and neutrophil fungicidal activity and macrophage function respectively [1, 2, 6]. Once identified, aggressive surgical management as well as a multi-disciplinary approach has been shown to reduce mortality [7].

Posaconazole delayed-release tablets were used after intravenous induction. Modelling based on TDM demonstrated AUC/MIC ratios which exceeded that shown to be sufficient for *Rhizopus oryzae* in a murine model [8]. Notwithstanding limited evidence, TDM is considered standard of care for posaconazole salvage therapy as an adequate AUC/MIC ratio cannot reliably be achieved even with the use of delayed-release tablets which have improved bioavailability and more predictable exposure [9].

Unfortunately, the patient developed severe hypomagnesemia. Posaconazole product information notes an 18% incidence of hypomagnesemia whereas that for isavuconazole is 5.4% [10]. Due to the disabling adverse effects despite apparent disease control, he was switched to isavuconazole, a novel second-generation triazole with broad-spectrum activity including Mucorales. Early clinical data demonstrate comparable efficacy between isavuconazole and amphotericin for the treatment of mucormycosis [11,12]. Although no significant post-marketing safety signal in this respect has emerged to our knowledge, given the QTc prolongation caused by posaconazole, physicians should be aware of the potential risk of cardiac arrest.

To our knowledge, this is the first report of hypomagnesaemia attributable to both posaconazole and isavuconazole. The mechanism of the hypomagnesaemia may be multifactorial, and part of a complex interplay between medications, cation channel receptors, intestinal absorption and urinary excretion of magnesium. Mutations in the transient receptor potential melastatin 6 (TRPM6) genes that encodes a cation channel have been linked to familial hypomagnesaemia [7]. Nephrotoxic drugs like amphotericin B can produce urinary magnesium wasting, and the residual tissue effects of the amphotericin B may have

compounded this effect when the azole was commenced [13]. While proton pump inhibitors can cause hypomagnesemia, due to inhibition of TRPM6 and 7 channels, leading to impaired intestinal cell absorption, our patient was never on this class of medication [14–16]. Ranitidine, which our patient was on, has been shown to reverse the effects of hypomagnesaemia due to this mechanism. A proposed mechanism of azole induced hypomagnesaemia may relate to unintended effects on cation channel receptors, leading to impaired magnesium absorption or excessive urinary excretion.

In summary, the antifungal treatment of mucormycosis presents several challenges related to adverse effects including renal impairment with liposomal amphotericin. Oral azole therapy represents a longer term strategy to manage this life threatening disease; however, unrecognised adverse effects such as hypomagnesaemia may complicate management. Our case suggests that both posaconazole and isavuconazole can be associated with severe symptomatic hypomagnesaemia, which has the potential to cause cardiac dysrhythmias, and that routine monitoring of magnesium levels while on azole therapy should be performed.

Acknowledgements

Isavuconazole was provided by Basilea pharmaceutica for compassionate use.

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