Acute kidney injury

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Acute kidney injury- an unusual complication of posaconazole use

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Abstract:	<p>Triazole antifungals are useful in the treatment of Aspergillus disease and these drugs have side effects which clinicians should be aware of. Posaconazole is an orally administered second-generation triazole antifungal agent which inhibits lanosterol 14-alpha-demethylase, an enzyme that converts lanosterol to ergosterol, a vital component of the fungal cell membrane. Posaconazole has a favorable side effect profile, is safe and well tolerated when compared to the earlier generation of triazole antifungals. Common side effects of posaconazole include gastrointestinal, hepatobiliary, neurological, and skin and subcutaneous disorders. Renal disorders are classed as an uncommon side effect of posaconazole, occurring in ~0.1-1% of patients.</p> <p>We describe 2 episodes of acute kidney injury (AKI) in a Caucasian whose Aspergillus lung disease was being treated with posaconazole. Regular monitoring of renal function may be necessary for patients on posaconazole to facilitate early identification of acute kidney injury which is reversible.</p>

Title page

Acute kidney injury– an unusual complication of posaconazole use

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Transparency statement:

Denning and family hold Founder shares in F2G Ltd., a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen, Quintilles, and Pulmocide. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck, and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group, and the British Society for Medical Mycology Standards of Care committee.

All other authors: none to declare

Abstract

Triazole antifungals are useful in the treatment of Aspergillus disease and these drugs have side effects which clinicians should be aware of. Posaconazole is an orally administered second-generation triazole antifungal agent which inhibits lanosterol 14-alpha-demethylase, an enzyme that converts lanosterol to ergosterol, a vital component of the fungal cell membrane. Posaconazole has a favorable side effect profile, is safe and well tolerated when compared to the earlier generation of triazole antifungals. Common side effects of posaconazole include gastrointestinal, hepatobiliary, neurological, and skin and subcutaneous disorders. Renal disorders are classed as an uncommon side effect of posaconazole, occurring in ~0.1-1% of patients.

We describe 2 episodes of acute kidney injury (AKI) in a Caucasian whose Aspergillus lung disease was being treated with posaconazole. Regular monitoring of renal function may be necessary for patients on posaconazole to facilitate early identification of acute kidney injury which is reversible.

Keywords: Posaconazole; acute kidney injury; Aspergillus; therapeutic drug monitoring; triazole

Introduction

Drug-induced nephrotoxicity is a common cause of acute kidney injury (AKI).¹ Nearly 300 different drugs from various classes are known to cause AKI.² AKI can cause significant long-term consequences including cardiovascular events, progression to chronic kidney disease and mortality.³

Posaconazole is an orally administered second-generation triazole antifungal agent which inhibits lanosterol 14- α -demethylase, an enzyme that converts lanosterol to ergosterol, a vital component of the fungal cell membrane. Posaconazole has a favorable side effect profile, is safe and well tolerated when compared to the earlier generation of triazole antifungals.⁴ Common side effects of posaconazole include gastrointestinal, hepatobiliary, neurological, and skin and subcutaneous disorders. Renal disorders are classed as an uncommon side effect of posaconazole, occurring in ~0.1-1% of patients.^{5,6} We report 2 episodes of AKI attributed to posaconazole therapy in the same patient.

Clinical details

A 74-year-old Caucasian male with a diagnosis of chronic cavitary pulmonary aspergillosis (CCPA) complicating allergic bronchopulmonary aspergillosis (ABPA) was managed in the National Aspergillosis Centre, University Hospital of South Manchester. The diagnosis of CCPA was made by a recognized combination⁷ of characteristics: a computed tomography (CT) thorax scan consistent with CCPA, direct evidence of *Aspergillus* infection from sputum cultures in addition to elevated *Aspergillus* IgG following the exclusion of some alternative diagnosis. In addition, his pulmonary disease had been present for greater than three months. His past medical history was significant for type II diabetes mellitus on metformin and adrenal insufficiency on steroid replacement. He was previously treated with itraconazole for ABPA for 2 years but this was switched to voriconazole following the development of radiological and serological features consistent with CCPA and loss of libido. He developed severe gastrointestinal adverse events and visual disturbances requiring discontinuation of

voriconazole therapy after 5 weeks (Figure 1). He was then switched to posaconazole tablets at a dose of 300mg once a day, which he took for a year with average serum levels of 2.1mg/l.

He was admitted in November 2016 due to an incidental finding of a serum creatinine rise from 102 $\mu\text{mol/L}$ to 159 $\mu\text{mol/L}$ with a reduction in his estimated glomerular filtration rate (eGFR) to 38mL/min, a urea of 13.6mmol/l, a potassium of 7.1mmol/L and no acute changes on his electrocardiogram. His liver function tests were also deranged with an ALT of 426IU/L and an alkaline phosphatase of 380IU/L. His posaconazole levels were within the therapeutic range at 1.81mg/l (measured by bioassay done using a mass spectrometer). Posaconazole was stopped and he was admitted and managed conservatively (Figure 1). His potassium fell to 5.9mmol/l over three days and he was discharged home. A renal ultrasound scan was normal.

Four months later, his serum *Aspergillus*-specific IgG had increased from 78mg/L to 390mg/L. In the light of this, posaconazole tablets were recommenced at a dose of 300mg once daily with weekly renal and liver function testing. Two weeks later he presented with pleuritic chest pain, shortness of breath and a productive cough. His serum electrolytes revealed a urea of 11.1mmol/l, a creatinine of 143mmol/l, an eGFR of 42 mL/min and potassium of 5.7mmol/l. Again, his posaconazole levels were therapeutic at 1.35mg/l. He was admitted and managed for recurrent AKI with hyperkalaemia. Posaconazole was stopped, his serum creatinine and potassium normalized over a one week period and he was subsequently discharged. Three months later, he was started on isavuconazole but this had to be discontinued after five months due to liver toxicity.

70 **Discussion**

71 Posaconazole has potent activity against *Aspergillus* species and is an effective agent for
72 the prevention and treatment of a range of invasive fungal infections. Felton *et al*⁶
73 reported the first use of posaconazole in the long-term treatment of 79 patients with
74 chronic pulmonary aspergillosis (CPA) in 2010. Adverse reactions were observed in 12
75 patients (15%) (nausea in 5, rash in 5, headache in 1, and lethargy in 1), leading to
76 discontinuation of treatment in 9 patients. In immunocompromised and critically ill
77 patients with refractory invasive fungal diseases, long-term (>6 months) therapy with
78 posaconazole was not shown to increase the risk of any individual adverse event. The
79 most common treatment-related adverse events in these patients were nausea (8%) and
80 vomiting (6%).⁸ Isavuconazole is a much newer novel triazole agent with utility in
81 treatment of CCPA that does not contribute to a prolonged QT interval, has fewer drug–
82 drug interactions; and does not require dose adjustments in patients with hepatic or
83 renal impairment.^{9,10}

84

85 From the foregoing, it would appear that prolonged posaconazole treatment is
86 associated with a generally favourable safety profile. However, our index patient
87 developed an AKI after oral administration of posaconazole with rapid improvement
88 following discontinuation of the drug on both occasions.

89 Posaconazole is predominantly metabolised and excreted through the liver; renal
90 clearance is a minor elimination pathway. Mild-to-moderate renal impairment has no

91 effect on the pharmacokinetics of posaconazole and thus no dose adjustment is
92 recommended.^{5,11} The oral bioavailability of delayed-release posaconazole tablets is
93 more predictable than that of the liquid suspension and higher plasma levels are
94 achieved with the tablets when compared to the liquid suspension.¹² It is recommended
95 that serum levels are monitored as some patients may not achieve the desired target.
96 However, the highest cut-off to prevent toxicity is not known. Another reason to
97 routinely monitor posaconazole serum levels is that there are large inter-individual and
98 intra-individual variations in the bioavailability of this compound. Therapeutic drug
99 monitoring (TDM) optimises drug exposure and improves clinical response to
100 antifungals.¹³ The mechanism of induction of AKI in triazole therapy is not
101 understood.¹⁴

103 **Conclusion**

104 Though uncommon, AKI can result from posaconazole use. Regular monitoring of renal
105 function may be necessary for patients on posaconazole to facilitate early identification
106 of AKI.

108 **Consent statement**

109 Consent to publish this article was obtained from the patient.

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Figure 1: Timeline of events

AKI: acute kidney injury; CCPA: chronic cavitary pulmonary aspergillosis; CT: computed tomography; GIT: gastrointestinal tract

Comment	Response
<p>Line 17</p> <p>- CCPA is a problematic pulmonary disease and diagnosis requires a combination of radiological and/or microbiological characteristics</p> <p>Specify diagnostic criteria employed, according to Denning DW (Eur Respir J, 2016), particularly if a direct evidence of Aspergillus infection was documented in this patient (in clinical details and in Discussion session)</p>	<p>The diagnostic criteria has been stated (see line 19-23)</p>
<p>-"ABPA" must be indicated in the line 17 (instead of in the line 21)</p>	<p>This has been done (see line 17)</p>
<p>Line 25-26: TDM posaconazole</p> <p>-Specify the bioassay used to measure TDM posaconazole tablets. Although safety data with this formulation in real life are insufficient, the clinical utility of posaconazole TDM approach may be more stressed (as recently reported by Boglione -Kerrien in hematological patients , J Cancer Res Clin Oncol 2018) in the Discussion</p>	<p>This has been addressed (see line 38 and line 77-83)</p>
<p>In the Discussion, also the role of new antifungal agents as isavuconazole in non neutropenic patients with diagnosis of CCPA , could be emphasized</p>	<p>This has been done (see line 63-66)</p>