The Use of Ketoconazole in Sarcoidosis Induced Hypercalcaemia

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Objectives/Background

Acute and chronic hypercalcaemia can have significant complications for patients and requires prompt treatment. This case highlights the use of ketoconazole for resistant sarcoidosis induced hypercalcaemia, and the role pharmacy played in its safe and appropriate use.

Sarcoidosis is a multisystem granulomatous disorder with unknown aetiology characterised by presence of non-caseating granulomas (non-necrotizing) these often surrounded by scar tissue.

The mechanism behind hypercalcaemia in granulomatous disorders has been mostly evaluated in sarcoidosis. The primary abnormality appears to be an increase intestinal calcium absorption induced by high serum calcitriol (1,25 dihydroxyvitamin D). The reduction in calcium mediated by ketoconazole is thought to be due to inhibition of 1alpha hydroxylase, a P450 enzyme, responsible for activation of vitamin D.[1,2]

Clinical Features

•:A 54 year-old-male was admitted for investigation of potential sarcoidosis and management of hypercalcaemia. His background included type 2 diabetes with multiple complications including chronic kidney disease, coronary artery disease and peripheral vascular disease with a previous left toe amputation. Additionally his background included dyslipidaemia, GORD and anxiety/depression.

His corrected serum calcium on admission was 3.45mmol/L and he was commenced on the standard of care glucocorticoid regime and intravenous fluids. Despite this however his calcium remained high and he began to suffer glucocorticoid adverse effects such as high BSLs, fluid retention and gastric discomfort.

He was therefore commenced on ketoconazole 200mg daily by the respiratory team.

Treatment Options

Hypercalcaemia and Hypercalciuria in Sarcoidosis

Intravenous Saline Hydration

- Severe (>3.5mmol/L) or symptomatic hypercalcaemia

Standard Of Care: Glucocorticoids

- Starting Dose 0.3-0.5mg/kg/day
- Maintenance dose: 5-10mg/d
- Total duration of treatment: at least 12 months

Alternatives

- Chloroquine
- Dose: 250-500mg/d
- Hydroxychloroquine
- Dose: 200-400mg/d
- Ketoconazole
- Dose: 600-800mg/d

Pharmacists Role

Supply

- Once considered safe, pharmacist organised supply through the Special Access Scheme

Drug interactions

- The pharmacist identified a number of drug interactions and provided recommendations
- Of note, being a dibasic compound ketoconazole's absorption is reduced substantially by PPIs and therefore dosing with an acidic beverage was recommended.
- Additionally being a 3A4 inhibitor caution was needed with his statin and lercandipine

Dose

- Evidence for the use of Ketoconazole is based on a number of case studies that utilised 600-800mg daily
- Patient was commenced on 200mg (standard dose) and did not improve, therefore pharmacist recommended a dose increase to treat inline with the available evidence

Ongoing Monitoring/Counselling

- Ketoconazole was pulled off the Australian market due to risk of hepatotoxicity
- Current guidelines recommend baseline and regular LFT monitoring
- Pharmacist organised with resident an outpatient appointment and advised team to ensure LFTs were checked regularly at these appointments

Interventions

Ketoconazole is a well known CYP3A4 inhibitor and is therefore notoriously involved in drug interactions. Being a weak dibasic compound, ketoconazole is insoluble in water except at a pH below 3 & therefore sufficient gastric acidity is required for dissolution and absorption.[3] Due to a history of gastritis and current prednisolone use, the patient required a PPI. Studies have demonstrated that co-administration of a PPI or H2 antagonist decreases absorption by 50%.[4] Some resources recommend the co-administration of an acidic beverage such as coke.[4] Whilst never specifically trialled, it has been theorised that any beverage with a pH of less than 3 would provide sufficient acidity to aid in ketoconazole's absorption. Therefore due to the patients history of type 2 diabetes, coke zero was recommended after researching it's pH (2.96) given its low sugar content.

Conclusion/Outcomes

Despite an initial decrease in calcium once ketoconazole had been commenced, it remained fairly stable above 3.0. The team's goal was to reduce the calcium to below 3.0 prior to discharge. After recommending the dose be increased to be in line with the available evidence the calcium dropped to 2.72 and the patient was discharged. He was then followed up in an outpatient clinic with his calcium in May being stable at 2.41 whilst still on the ketoconazole. Most case reports stated a duration of 6 -12 months with the patient being reviewed in clinic again in November 2018. This case therefore highlights not only the use of ketoconazole for hypercalcaemia secondary to sarcoidosis but the necessary safety and efficacy considerations if it is to be used effectively.

References

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