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Bedaquiline overdose: a case report.

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Highlights

- Bedaquiline is a new anti-tuberculosis medication used for treatment of drug resistant infections
- We report a case of a man receiving an overdose of bedaquiline for 60 days through medical error, no concerning findings were seen.
- Bedaquiline dosing schedule is complex requiring attention to correct administration

Summary

We present a case report describing outcomes in a 21 year old HIV-negative man who received treatment with bedaquiline. Due to error, dosage received comprised 4 pills of 100mg every second day in the 60 days following the first two weeks of 4 pills of 100mg every day. On detection, treatment was continued as per standard dosing of 200mg given three times per week, with enhanced monitoring of ECG and liver function. The man was asymptomatic, with no signs of jaundice, abdominal pain, or abnormal heart rhythm. Toxic effects at this dosage were therefore not observed.

Keywords: Tuberculosis, Bedaquiline, Adverse Events, Therapeutic Index, Tolerability

Introduction

Bedaquiline (Bdq), a new anti-tuberculosis (TB) drug from the diarylquinoline group, shows promise for treatment of multi-drug resistant tuberculosis (MDR-TB). In 2013 Bdq was approved by multiple regulatory authorities including the European Medicines Authority and the US Food and Drug Administration. Currently Bdq being used mainly in patients with

limited treatment options due to resistance or toxicity to second-line anti-TB drugs.¹

During Phase 1 and Phase 2 clinical trials the main adverse events (AEs) identified were extension of corrected QT (QTc) interval and elevation of liver enzymes.^{2,3} Bdq has a prolonged half-life; mean half-life after 8 weeks of treatment 164 days for Bdq, and 159 days for M2³ active metabolite. Bdq is registered for a treatment duration of 24 weeks. During the first 2 weeks, recommended dosing is 4 pills of 100mg every day, then 2 pills of 100mg 3 times per week.¹

We report a case of overdose in a patient who received 4 pills of 100mg every 2nd day, in the 60 days after the first two weeks of treatment. The patient participated in the observational trial of short standardised MDR-TB treatment regimen of 9-12 months in Maputo, Mozambique.⁴

Case report

A 21 year old HIV-negative man, diagnosed with rifampicin resistant TB using GeneXpert, had started treatment with kanamycin (Km), moxifloxacin (Mfx), clofazimine (Cfz), prothionamide (Pto), ethambutol (E), pyrazinamide (Z) and

isoniazid (H). All drugs were administered in standard dosages, except Mfx and H which were given in high-dosing - 800 mg and 1000mg daily, respectively.

The patient received medications as an outpatient under daily direct observation. A nurse was responsible for drug administration, with review by a medical doctor on a monthly basis or more often if required. Clinical monitoring and follow-up were done monthly, including electrocardiogram (ECG), audiometry and other laboratory investigations. Baseline investigations revealed a Hb=9.9 g/dl, other results were normal, QTc (Fredericia) of 396 ms. The patient had no other comorbidities and was not taking any other medications.

10 weeks later the patient was diagnosed with grade 2 hearing loss by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS) attributed to the use of Km. Hearing loss continued to worsen and after 1 month the Km was replaced with Bdq as permitted within the study protocol. All other drugs remained the same, with no dose modification.

After 2 months of this regimen, the nurse administering the medications reported to the treating doctor that the available doses which should have lasted six months, were finished. A detailed history from the patient and nurse revealed that after two weeks of a 400 mg loading dose daily, the patient had taken 400mg Bdq 4 times per week, instead of 200mg three times per week.

The patient had good adherence and there were no missed doses. During medical evaluation the patient was asymptomatic and clinically stable and no jaundice, abdominal pain, or abnormal heart rhythm were detected. The most recent ECG from 3 days prior showed a QTcF of 411 ms (see table 1).

The case was discussed with experts and the decision was taken to continue the treatment with Bdq reduced to standard dosing of 200mg given 3 times per week. The rest of the regimen was continued without modification.

The case was reported to the MSF pharmacovigilance committee, national authorities and the manufacturer of Bdq. Increased clinical review and monitoring of QTc and aminotransferases were performed.

Long term exposure to higher than the recommended Bdq dose was not observed to lead to cardio-toxic or hepatotoxic effects in this patient. Minor asymptomatic elevation of AST fit the definition of DAIDS score grade 1 hepatotoxicity and did not require medical intervention.

The patient culture converted after 3.5 months, before introduction of Bdq, and remained culture negative. After six months of treatment with Bdq and

nine months since the beginning of treatment, the patient was classified as outcome cured and treatment was completed.

Discussion

This case suggests that the therapeutic index – the dose range between therapeutic and toxic dosages - for Bdq may not be narrow. We describe a young patient who took Bdq in higher dosages and more frequently than recommended due to a medical error. The patient remained asymptomatic with no concerning findings on monitoring. The patient did not have QTc prolongation despite being on 3 potentially QT prolonging medications, including standard dosing of Cfz and a higher than standard dosing of Mfx.

There are limited data on tolerability of high doses of Bdq; current data focuses on the effects of short term exposure. An industry sponsored study did not find significant QTc prolongation after a single dose of 800mg Bdq.⁶ No Bdq toxicity was observed in an extended early bactericidal activity study using a loading dose of 700mg on day 1, 500 mg on day 2 and continuation of 400mg

daily for 14 days.² The optimal dose for Bdq is not yet known and current trials are examining dosing of 200 mg daily for 8 weeks followed by 100mg daily.⁷

Out of the three drugs that are known to prolong the QT interval, Bdq and Cfz have a long half-life (6 and 2.5 months respectively), so only cessation of Mfx (half-life 6 hours) could significantly reduce QTc prolongation risks in a short time period. At the same time Mfx is one of the most effective drugs against MDR TB. Three possible management scenarios were discussed by the medical team:

- Cessation of Bdq
- Withholding Bdq for a short period and then restart at correct dosing (with or without suspension of other QT prolonging drugs).
- Changing Bdq to the correct dosing of 200 mg three times per week without stopping or suspending Bdq or other QT prolonging drugs.

As bacteriological results informing culture conversion were not available at the time of the decision, concerns were raised that if Bdq or other drugs were ceased, the remaining regimen could be too weak to ensure effective treatment. The second scenario which allows high-drug levels to decrease to safe levels likely would have been chosen by the medical team if any toxic

effects of the overdose was observed. Because the patient showed no signs of toxicity of Bdq at the higher dose, the medical team chose option three.

Conclusion

In this patient, two months of treatment with approximately double the recommended dose of Bdq were not associated with any toxic effects, even in combination with other drugs known to prolong the QT interval. While more evidence is needed, toxic doses of Bdq may be substantially higher than the present recommended dosing levels.

Role of the funding source

MSF Switzerland is financing the research on short MDR-TB treatment and provision of all drugs as per protocol including Bedaquiline as well as publication.

Ethical approval

The observational study of short standardised MDR-TB treatment regimen of

9-12 months in has been approved by the ethical review board of MSF and the national ethical review board of the ministry of health Mozambique.

Declaration of interests:

Oleksandr Telnov: Yes. Dr. Telnov reports that he does research on bedaquiline and other drugs mentioned in the article under support from UNITAID for the endTB trial.

Veronica Alvarez, Elena Gradila, Lucas Molfino: none

Philipp du Cros: Yes Dr. du Cros reports that he was a member of the Steering Committee for the TB PRACTECAL randomised clinical trial for MDR-TB sponsored by Médecins Sans Frontières (MSF) from 2013 to 2017.

Michael Rich: Yes. Dr Rich reports that he does research on bedaquiline and other drugs mentioned in the article under support from UNITAID for the endTB Project.

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Table 1: ECG and LFT results

| Days on treatment | Treatment | QTcF (<450msec) | AST (<40 U/L) | ALT (<56 U/L) |
|-------------------|---------------------------|--------------------|------------------|------------------|
| Baseline | Regimen commenced | 396 msec | 42 U/L | 22 U/L |
| Day 39 | | 387 msec | 11 U/L | 19 U/L |
| Day 52 | | - | 36 U/L | 25 U/L |
| Day 96 | | 437 msec | 31 U/L | 21 U/L |
| Day103 | | 414 msec | - | - |
| Day104 | Bdq commenced | | | |
| Day117 | | 420 msec | 31 U/L | 23 U/L |
| Day152 | | 415 msec | 20.4 U/L | 16.5 U/L |
| Day 179 | | 411 msec | 18.5 U/L | 26 U/L |
| Day 182 | Overdose of Bdq detected. | | | |
| Day 201 | | 389 msec | 40 U/L | 25.6 U/L |
| Day 243 | | 406 msec | 46 U/L | 31 U/L |

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| Day 266 | | - | 20 U/L | 16 U/L |

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