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2016

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Publication Details

Lindsay, P. J., Bond, S. E., Norris, R., Marriott, D. J. E. & Miyakis, S. (2016). Posaconazole therapeutic drug monitoring in a regional hospital setting. *Therapeutic Drug Monitoring*, 38 (6), 804-807.

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Posaconazole therapeutic drug monitoring in a regional hospital setting

Abstract

BACKGROUND: Posaconazole therapeutic drug monitoring (TDM) is recommended to promote effective antifungal prophylaxis, but its utility has yet to be optimized. Breakthrough invasive fungal infections have been reported with serum concentrations/L, but there is little evidence to determine the optimal serum concentration for efficacy or concentrations associated with toxicity. Challenges for effective monitoring are greater in settings without posaconazole TDM facilities because of the long turnaround time before receipt of results.

METHODS: Thirty-eight TDM episodes were performed on 18 patients in a regional center in Australia during a 30-month period. Australian guidelines recommend a trough serum concentration of ≥ 700 mcg/L. The response to concentrations below the recommendation threshold (700 mcg/L), the final serum plasma concentration for each patient, and the appropriateness of TDM were evaluated.

RESULTS: A total of 19 (50%) concentrations were recorded to be < 700 mcg/L. Of these 19 concentrations, the drug dose was increased on only 4 occasions. Eleven of 18 patients (61%) had initial concentrations

CONCLUSIONS: The results demonstrate a lack of confidence and consistency in ordering, interpreting, and following up posaconazole concentrations. Therefore, the use of TDM should be carefully considered, especially in regional centers. Such settings should consider the practicalities of posaconazole TDM and try to improve the process to ensure consistency and optimization of patient care.

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

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Posaconazole therapeutic drug monitoring in a regional hospital setting

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Abstract

Background: Posaconazole therapeutic drug monitoring (TDM) is recommended to promote effective antifungal prophylaxis, but its utility has yet to be optimized. Breakthrough invasive fungal infections have been reported with serum concentrations $<700\text{ }\mu\text{g/L}$, but there is little evidence to determine the optimal serum concentration for efficacy or concentrations associated with toxicity. Challenges for effective monitoring are greater in settings without posaconazole TDM facilities due to the long turnaround time prior to receipt of results.

Methods: Thirty-eight TDM episodes were performed on 18 patients in a regional center in Australia during a 30-month period. Australian guidelines recommend a trough serum concentration of $\geq 700\text{ }\mu\text{g/L}$. The response to concentrations below the recommendation threshold ($700\text{ }\mu\text{g/L}$), the final serum plasma concentration for each patient, and the appropriateness of TDM were evaluated.

Results: A total of 19 (50%) concentrations were recorded to be $<700\text{ }\mu\text{g/L}$. Of these 19 concentrations, the drug dose was increased on only 4 occasions. Eleven out of 18 patients (61%) had initial concentrations $<700\text{ }\mu\text{g/L}$, with only 3 (27%) among those achieving final concentration $\geq 700\text{ }\mu\text{g/L}$; 5 patients with initial concentrations $<700\text{ }\mu\text{g/L}$ did not have any further TDM testing. Nine of the 18 (50%) patients had a final concentration $<700\text{ }\mu\text{g/L}$. Five out of 7 (71%) patients with initial concentrations $\geq 700\text{ }\mu\text{g/L}$ had further TDM with no reasoning documented.

Conclusions: The results demonstrate a lack of confidence and consistency in ordering, interpreting, and following up posaconazole concentrations. Therefore, the use of TDM should be carefully considered, especially in regional centers. Such settings should consider the practicalities of posaconazole TDM and try to improve the process to ensure consistency and optimization of patient care.

Keywords: posaconazole, drug monitoring, prophylaxis, antifungal agent

Introduction

Posaconazole is an extended spectrum azole used for the treatment of invasive fungal infections (IFIs). It is recommended as first-line prophylaxis during leukemia induction treatment, prolonged neutropenia, and graft-versus-host disease.[1]

The understanding of the exposure-response relationship in posaconazole prophylaxis is improving; however, therapeutic drug monitoring (TDM) may be an important tool to maximize efficacy.[2] The risk for each patient is dynamic and depends on host factors, target organisms, associated interventions, and hospital setting.[3] Pharmacokinetic properties of posaconazole (poor water solubility necessitating ingestion with a high-fat meal; absorption at low intestinal pH requiring acidic meals) and potential drug interactions further complicate absorption, which is evident with the oral suspension.[4] Use of the newer once-daily tablet formulation results in more consistent serum concentrations than the three times daily oral suspension.[5]

The Australian guidelines recommend posaconazole concentrations ≥ 700 $\mu\text{g/L}$ during prophylaxis.[6] Lower concentrations (between 500 and 700 $\mu\text{g/L}$) have been associated with breakthrough invasive fungal infections (IFIs).[7] However, the optimal posaconazole concentration during prophylaxis is not defined,[8] which makes real-time data to monitor concentrations crucial.[9] For patients managed within a reference center (i.e., metropolitan hospitals with posaconazole TDM facilities on-site), TDM can guide timely and appropriate drug dosage modifications. Previous clinical TDM studies have been conducted in such reference centers.[10-12] Those studies have shown that dose modification has resulted in more appropriate levels. Outside those settings, practical limitations on clinician access to results and time lag until dose adjustment risk reducing the utility of the process.[13] Very limited data exist on the value of posaconazole TDM in regional hospitals without posaconazole TDM facilities.[14]

The aim of the study was to evaluate the utility of posaconazole TDM for prophylaxis in a regional hospital without on-site TDM facilities.

Materials and Methods

This retrospective analysis was performed at Wollongong Hospital in New South Wales (NSW), Australia, a 600-bed academic medical center where neither solid organ nor allogeneic bone marrow transplants are performed. Between January 2013 and June 2015, all concentrations recorded from hospitalized patients receiving posaconazole prophylaxis were analyzed. Any TDM episodes from patients transferred to another hospital or from outpatients were excluded, due to lack of data. In April 2015, the modified release tablet was introduced, with 4 patients receiving tablets (300 mg once daily) and 14 receiving oral suspension (200 mg three times per day); two patients changed from suspension to tablets. Wollongong Hospital has no on-site analysis of posaconazole concentrations, with the NSW State Reference Laboratory located 70 km away at St Vincent's Hospital, Sydney. Serum posaconazole concentrations were collected at the hematologists' discretion. The turnaround time for results varied from 3 to 7 days, with samples processed on Mondays, Tuesdays, and Thursdays. Posaconazole concentrations were matched with the patient's paper and electronic medical records (eMR), which were analyzed to determine whether the concentrations were documented and whether the dose was changed as a result.

Outcome measures included breakthrough IFIs, reported side effects from posaconazole, the number of posaconazole concentrations ≥ 700 $\mu\text{g/L}$, the number of documented dose changes in response to concentrations below the recommendation threshold (700 $\mu\text{g/L}$), the final serum plasma concentration for each patient, and the appropriateness of TDM. TDM was deemed inappropriate if concentrations were ≥ 700 $\mu\text{g/L}$ with all the following conditions: no new change in medication or nutritional status, no clinical signs of toxicity, and <3 months since the last TDM episode. If the concentration was <700 $\mu\text{g/L}$ with no follow-up TDM episode, management was also regarded as inappropriate.

Posaconazole concentrations were performed in the setting of standard patient care, therefore Ethics Approval was not necessary.

Results

Thirty-eight posaconazole TDM episodes were performed on 18 hematology inpatients (Table 1). Overall, 19/38 posaconazole concentrations (50%) were below the recommended threshold for prophylaxis (Figure 1) (median 358 µg/L; range 40-669 µg/L). Of those, only 4 (21%) had a dose increase in response to the low concentration. The remaining 19 concentrations were >700 µg/L (median 1035; range 708-4028).

Eleven (61%) patients had initial concentrations <700 µg/L. Only 3 (27%) had a final concentration above 700 µg/L. In total, 9 (50%) patients had final concentrations <700 µg/L (Figure 1).

Among the 11 patients whose initial posaconazole concentration was <700 µg/L, 5 (46%) did not have a follow-up TDM. Among the 7 patients with initial posaconazole concentration ≥700 µg/L, 5 (71%) had a subsequent TDM episode without clear documented rationale (i.e., dose changes, new medications and/or concerns of interactions, patient symptoms suggesting toxicity, change in clinical condition or nutrition status).

Overall, among the 38 TDM episodes, 5 patients had an initial concentration <700 µg/L with no further follow-up. Nine TDM episodes from 5 patients with concentrations >700 µg/L were undertaken without documented reasoning. Nine (50%) of the 18 final concentrations were <700 µg/L, possibly placing those patients at risk of IFI.

Two patients died in hospital (one from pneumonia and one from biliary sepsis). No patients developed proven IFI during the study period or demonstrated any side effects attributed to posaconazole.

There was no difference in the proportion of concentrations between the oral suspension (31 concentrations, 16 below threshold) and the tablet (7 concentrations, 4 below threshold).

Discussion

Despite the recommendation of utilizing TDM for patients receiving prophylactic posaconazole,[6, 15] our study has identified barriers to appropriate TDM in a regional hospital without posaconazole TDM facilities. These include challenges in results retrieval, long turnaround time, and the variable interpretation of optimal serum concentrations.

The Australian guidelines recommend posaconazole oral suspension dosing of 200 mg three times daily;[1] half of the TDM episodes performed on this dose yielded concentrations $<700\text{ }\mu\text{g/L}$. Only 21% of doses were changed in response to the low concentrations. None of these patients' follow-up concentrations were $>700\text{ }\mu\text{g/L}$, and none of them had further follow-up despite persistent low levels. With posaconazole therapy having high intra-patient and inter-patient variability, the initial serum plasma concentrations may fluctuate.[8] Concentrations below the recommended threshold for prophylaxis ($<700\text{ }\mu\text{g/L}$) would be expected to be followed up. However, almost half of those patients had no further TDM episodes, and less than a third had their final concentrations $\geq 700\text{ }\mu\text{g/L}$. Those patterns argue that a lack of consistency in concentration interpretation exists, with potential implications for patient safety from suboptimal prophylaxis such as IFIs, although no proven IFIs were recorded in our small sample. The inconsistency in TDM practice was further outlined by the fact that the majority of patients with concentrations $\geq 700\text{ }\mu\text{g/L}$ underwent further testing, with no rationale documented.

An area of concern was the low concentration levels for patients receiving the tablet formulation. The variable documentation of the timing of blood sampling, proton pump inhibitor use, and dietary intake limited the opportunity to evaluate the reason for these low concentrations. The decision-making diagram (Figure 2) and site-specific education have been designed to improve TDM practice and documentation.

Although there is a lack of literature on posaconazole TDM in regional settings, difficulties associated with laboratory result turnaround time have been highlighted. [13] Other non-reference centers may be using posaconazole without TDM, due to logistic barriers. Our study site is relatively

close to the state reference center. Therefore, our findings would be expected at a greater scale for more remote centers.

The small number of patients is one of the study limitations. Outpatients (with a lower requirement for fast turnaround times) and patients transferred to another facility were excluded. The retrospective nature of this study often limited the information about circumstances surrounding TDM sampling and evaluation of low levels (i.e., trough or steady-state status, medication, or major nutritional changes), parameters that might have been known to the treating physicians but not necessarily documented in the notes. Results may have been considered less relevant due to the long turnaround times. Access to the results, which were not available online, required a phone call to the reference laboratory, risking a delay in appropriate actioning and increasing the time commitment of clinicians involved.

Unnecessary costs may be incurred due to inappropriate posaconazole TDM. This may be through both direct costs (for analysis, equipment, courier), and indirect costs (related to drawing the sample and time taken to follow up on results). Furthermore, patients may undergo redundant tests, increasing the risk of iatrogenic complications and causing unnecessary stress.

The findings from this study were presented to the managing hematologists of our hospital; the conclusions were discussed and optimal practices were agreed; a local protocol to optimize posaconazole TDM ordering and follow-up was designed as a result (Figure 2). Further research should be conducted to evaluate whether such protocols improve TDM practices in regional hospital settings.

Conclusion

Our results demonstrate an inconsistent approach to TDM ordering, interpretation, and subsequent actioning in a regional hospital setting. Evaluation of posaconazole use and TDM ordering in settings without TDM facilities should aim to identify challenges and particularities in each setting. Incorporation of site-specific protocols can be developed to optimize use and concurrently maximize patient safety.

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Table 1. Characteristics of Patients and Posaconazole Therapeutic Drug Monitoring (TDM)

Episodes

Patients	18
Female	11 (61%)
Age, Median (Range)	56 (18-88)
Condition	
- acute myeloid leukemia	14
- acute lymphoblastic leukemia	2
- chronic lymphocytic leukemia	1
- lymphoma	1
TDM per patient, median (range)	2 (1-6)
Patients with >1 TDM episode performed	10

Figure 1: All serum plasma concentrations and analysis of the final and initial serum posaconazole concentrations. Trough serum posaconazole ≥ 700 µg/L is the currently recommended target concentration for prophylaxis in Australia[6]

Figure 2: Recommended decision flow diagram provided for posaconazole therapeutic drug monitoring (TDM) in a regional hospital with Infectious Diseases Support and no on-site TDM facilities. Trough serum posaconazole ≥ 700 $\mu\text{g/L}$ is the currently recommended target concentration for prophylaxis in Australia[6]