Too Much of a Good Thing?
The Clinical Effects of Very High Serum Posaconazole Levels

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ABSTRACT

BACKGROUND
Posaconazole therapeutic drug monitoring (TDM) is widely utilized to assess therapeutic efficacy and safety (i.e., hepatotoxicity, QTc prolongation); however, little is known about clinical effects of very high serum posaconazole serum levels (i.e., ≥ 5000 ng/mL). Reported incidence rate of adverse drug reactions (ADRs) with posaconazole per most recent clinical trial was ~30%. The primary objective was to compare the ADR incidence in patients with serum posaconazole levels of 3000-4999 ng/mL to ≥5000 ng/mL.

METHODS
This retrospective cohort study included adult patients with a posaconazole serum level ≥3000 ng/mL from 1/1/2019 to 04/30/2021. The primary outcome was symptomatic ADR at time of first serum level ≥3000 ng/mL. Secondary outcomes were laboratory defined hepatoxicity, electrolyte and adrenal laboratory abnormalities, QTc changes, and dose changes in response to TDM. Patient outcomes were censored after the first serum level and were compared between groups using Fisher's exact tests.

RESULTS
Ninety patients met inclusion criteria, eighty with a level of 3000-4999 ng/mL and 10 with a level of ≥ 5000 ng/mL occurring at a median of 91 days (26-443) and 27 days (12-45) from posaconazole initiation, respectively. Majority of patients were immunocompromised (55.6% transplant recipients, 28.9% active malignancy, 5.6% other) with a split of treatment (50%) and prophylaxis (42.2%) indication. Symptomatic ADRs were very common in patients with posaconazole levels of ≥5000 ng/mL and 3000-4999 ng/mL (80% vs. 58.8%; p=0.31), primarily neurologic (49.1% overall) followed by gastrointestinal (32.7% overall). Hepatotoxicity was also common (≥5000 ng/mL 40% vs 3000-4999 ng/mL 23.4%, p=0.26). Fifty percent of patients had the posaconazole dose continued without change. Electrolytes and QTc results were similar between groups, but median overall QTc was borderline high (456 [IQR 435, 479]).

CONCLUSIONS
There are safety concerns for patients with serum posaconazole levels ≥3000 ng/mL. Posaconazole levels should be monitored and, importantly, dose adjusted according to serum level and patient symptoms for both treatment and prophylaxis indications.

BACKGROUND

- TDM and clinical response assessment are recommended for posaconazole given substantial variability in bioavailability and drug-interactions between individual patients.[1]
- Higher posaconazole concentrations have been associated with secondary hypertension and hypokalemia, consistent with pseudohyperaldosteronism.[2,3]
- In clinical trials, treatment emergent and treatment related ADR to posaconazole were 98% and 30%, respectively, with increased ALT or AST values, nausea and vomiting, and hypokalemia most frequently observed.[4]

METHODS

DESIGN: Retrospective, single center analysis

INCLUSION: Patients ≥ 18 years of age with a posaconazole level ≥ 3000 ng/mL from 1/1/2019 to 04/30/2021

EXCLUSION: Patient outcomes were censored after the first serum posaconazole level ≥3000 ng/mL

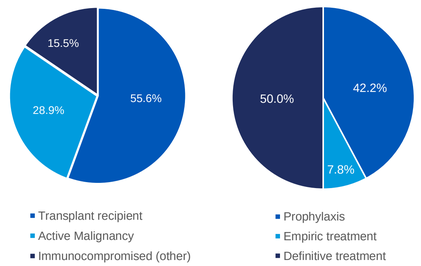
STATISTICS: Patients with posaconazole levels of 3000-4999 ng/mL and ≥5000 ng/mL were compared using Fisher's exact tests.

PRIMARY OUTCOME: Documented symptomatic adverse drug reactions at the time of first posaconazole level ≥3000 ng/mL

SECONDARY OUTCOMES: Hepatotoxicity, electrolyte and adrenal laboratory abnormalities, QTc changes, and dose changes in response to TDM

STUDY POPULATION

FIGURE 1: Patient Characteristics & Posaconazole Indication



RESULTS

FIGURE 2: Symptomatic ADR Incidence

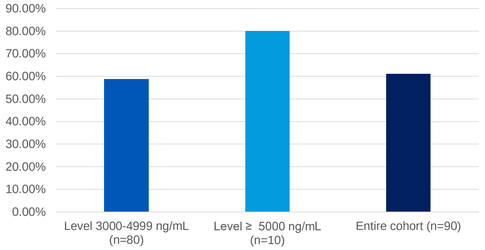


FIGURE 4: Hepatotoxicity Incidence

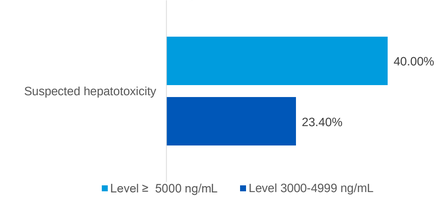


TABLE 1: Posaconazole Serum Levels and Dosing

	3000-4999 ng/mL (n=80)	≥5000 ng/mL (n=10)
Weight, median [IQR]	73 [59-87] kg	53 [49-69] kg
BMI, median [IQR]	25 [21.6-29.3]	20.7 [19.7-23.5]
Supratherapeutic level, median [IQR]	3580 [3150-3960] ng/mL	6140 [5540-7040] ng/mL
Level timing from initiation, median [IQR]	91 [26-443] days	27 [12-45] days
Posaconazole formulation		**n=90**
Tablet (delayed release)		96.7%
Other (IV or solution)		3.3%
Posaconazole dosing		
Loading dose		27.3%
Initial daily dose, median		300 mg
Current daily dose, median [range]		300 mg [200-800 mg]

FIGURE 3: ADR by Organ System

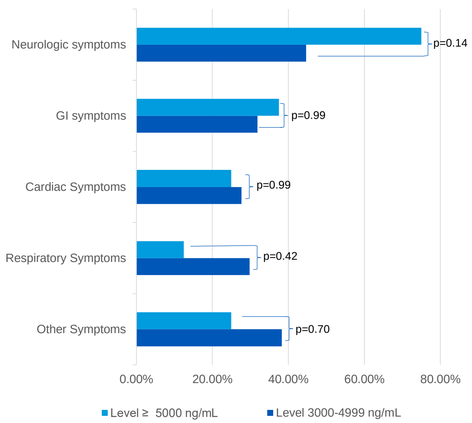
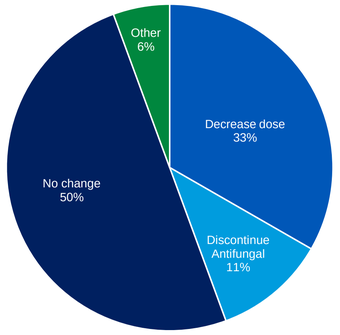


FIGURE 5: Posaconazole Dose Change Due to TDM



Repeat posaconazole level completed for 70% of patients following initial supratherapeutic level

RESULTS (CONTINUED)

Table 2: Laboratory and ECG Monitoring

Labs	Baseline	Elevated level
Potassium, median [IQR]	4.3 [3.9-4.5] mmol/L	4.0 [3.6-4.6] mmol/L
Bicarbonate, median [IQR]	23 [22-26] mmol/L	25 [23-27] mmol/L
ALT, median [IQR]	22 [16-36] U/L	31 [20-44] U/L
AST, median [IQR]	23 [19-37] U/L	29 [22-43] U/L
Total bilirubin, median [IQR]	0.4 [0.2-0.5] mg/dL	0.5 [0.3-0.6] mg/dL
Alk Phos, median [IQR]	87 [70-121] U/L	90 [74-130] U/L
QTc, median [IQR]	442 [427-463] ms	456 [435-479] ms

CONCLUSIONS

- **Supratherapeutic posaconazole levels >3000 ng/mL were associated with symptomatic adverse drug reactions.**
- Posaconazole levels should be monitored, and dosing should be adjusted according to serum levels and ADRs.

REFERENCES

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