Undetectable Everolimus Level from Probable Drug–Drug Interaction with Phenobarbital

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BACKGROUND: Phenobarbital is a known inducer of the cytochrome (CY) P450 enzyme system, with potent effects on the 3A4 enzyme.

OBJECTIVE: To describe a case of an undetectable everolimus level in a patient with renal-cell carcinoma who was also receiving phenobarbital.

DISCUSSION: A 53-year-old man was admitted to the hospital for decompensated heart failure. His medical history included hypertension, hyperlipidemia, renal-cell carcinoma, tobacco use, and a remote seizure disorder. Review of his preadmission medication list showed that a drug interaction may exist between everolimus and phenobarbital. The patient’s everolimus trough level was undetectable. Everolimus is extensively metabolized via CYP450 3A4 (CYP3A4). Although phenobarbital is expected to increase the metabolism and elimination of everolimus, no studies have been conducted to evaluate the extent of this interaction. According to the Drug Interaction Probability Scale, this drug–drug interaction is “probable.”

CONCLUSION: When significant drug interactions with potent CYP3A4 inducers cannot be avoided, a dose increase of everolimus may be warranted, and sampling of trough levels may be considered.

Case Report

A 53-year-old white man with a history of hypertension, hyperlipidemia, tobacco use, and a remote seizure disorder was diagnosed with renal-cell carcinoma in February 2016. After diagnosis, he underwent a left radical nephrectomy with evidence of tumor-free margins. The patient’s tumor measured 4.8 cm, and pathology analysis showed staging consistent with pathologic growth into the renal vein with unassessed regional lymph nodes (pT3aNx).

Three months later, the patient presented to our tertiary care center with shortness of breath and was found to have pleural metastases. Treatment was initiated with sunitinib 50 mg daily for 4 weeks of a 6-week treatment cycle. Two weeks later, the patient presented for a computed tomography scan of the chest, which revealed extensive interval worsening of metastatic disease. Shortly thereafter, he was admitted to the hospital for acute decompensated heart failure of unknown etiology, which was thought to be a potential side effect of sunitinib. After 6 weeks of sunitinib treatment, the treatment was switched from sunitinib to everolimus 10 mg daily.

In October 2016, the patient was readmitted for decompensated heart failure. His medications (taken at home) at the time included everolimus 10 mg daily; metoprolol succinate 100 mg daily; furosemide 120 mg twice daily; senna 8.6 mg plus docusate sodium 50 mg 2 tablets twice daily; and phenobarbital 240 mg nightly, which he had been taking for more than 20 years for his remote seizures. In addition, he recently started treatment with gabapentin 300 mg 3 times daily, a lidocaine patch 5% applied to the skin once daily, and hydromorphone 4 mg to 6 mg every 3 hours, as needed, for new-onset neoplasm-related pain.

A review of his laboratory test results at presentation indicated that the patient’s serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, and bilirubin levels were within normal range. Evaluation of his preadmission medication list revealed a potential drug interaction between everolimus and phenobarbital.

Subsequently, an everolimus serum trough level was sent to the laboratory. The results came back 3 days later, revealing a serum level of everolimus that was undetectable. To avoid further drug interaction, phenobarbital was discontinued, and levetiracetam 500 mg twice daily was started for seizure prevention. In addition, the patient was switched back from everolimus to sunitinib.

Discussion

Phenobarbital is a known inducer of the cytochrome (CY) P450 enzyme system with potent effects, in par-
Everolimus and Phenobarbital Potential Drug–Drug Interaction

Assessing the Potential Drug–Drug Interaction Between Phenobarbital and Everolimus, Using the Drug Interaction Probability Scale

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous credible reports of this interaction in humans?</td>
<td>N/A</td>
<td>0</td>
<td>No known reports</td>
</tr>
<tr>
<td>Is the observed interaction consistent with the known interactive properties of precipitant drug?</td>
<td>Yes</td>
<td>1</td>
<td>Phenobarbital is a potent CYP3A4 inducer</td>
</tr>
<tr>
<td>Is the observed interaction consistent with the known interactive properties of object drug?</td>
<td>Yes</td>
<td>1</td>
<td>Everolimus is extensively metabolized by CYP3A4</td>
</tr>
<tr>
<td>Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?</td>
<td>Yes</td>
<td>1</td>
<td>Detectable drug levels of everolimus would be expected at steady state (after 5 days of therapy)</td>
</tr>
<tr>
<td>Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?</td>
<td>N/A</td>
<td>0</td>
<td>Both drugs were discontinued simultaneously</td>
</tr>
<tr>
<td>Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?</td>
<td>N/A</td>
<td>0</td>
<td>No dechallenge was attempted</td>
</tr>
<tr>
<td>Are there reasonable alternative causes for the event?</td>
<td>No/Unknown</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?</td>
<td>Yes</td>
<td>1</td>
<td>Everolimus level was measured and reported as undetectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from previous question)?</td>
<td>No</td>
<td>0</td>
<td>No other evidence of the interaction was found except the undetectable everolimus level</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td>Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?</td>
<td>Unknown</td>
<td>0</td>
<td>There was no change in the precipitant drug dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td></td>
<td></td>
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</tbody>
</table>

- Adapted from reference 7.
- The Drug Interaction Probability Scale assigns each score a probability category related to an adverse drug reaction using the following ranges: highly probable, if the score is >8; probable, score of 5-8; possible, score of 2-4; doubtful, score of <2.
- CYP3A4 indicates cytochrome P450 3A4, N/A, not applicable.

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Table

Although we could consider the possibility of CYP3A4 induction caused by phenobarbital.

Another potent CYP3A4 inducer, rifampin, has been implicated in the findings of subtherapeutic everolimus levels in the transplant population in people using both drugs.1-6 In one published case, a patient started therapy with everolimus 0.5 mg twice daily, which resulted in everolimus trough blood level of 12 ng/mL.4 When rifampin was added to the patient's treatment regimen, the everolimus dose was titrated from 0.5 mg twice daily to 8 mg 3 times daily, with subsequent levels of everolimus remaining below 5 ng/mL.4 In addition, in an open-label crossover study of 12 patients receiving rifampin and everolimus, rifampin decreased the everolimus peak concentration by an average of 52% and the area under the curve by an average of 63%. The study investigators found significant variability between patients.6 A similar phenomenon may be expected with concomitant use of phenobarbital and everolimus.

The potential drug–drug interaction between phenobarbital and everolimus in our patient was assessed based on the Drug Interaction Probability Scale.7 Applying evidence from our case, the interaction between the 2 drugs resulted in a score of 5, signifying a “probable” drug interaction (Table).

One factor that likely reduced the score from “highly probable” (ie, a score >8) to “probable” (ie, a score of 5-8) is the simultaneous discontinuation of phenobarbital and everolimus; we were unable to evaluate everolimus levels in this patient without the presence of 3A4 induction caused by phenobarbital.

We evaluated alternative causes for the undetectable level of everolimus. Altered drug metabolism and clearance were unlikely, because the patient had adequate renal and hepatic function. The patient brought into the hospital his at-home supply of everolimus and demonstrated knowledge of, and compliance with, his medications. His drug regimen was reviewed for alteration of the 3A4, 1A2, 2A6, 2B6, 2C8, 2C9, and 2C19 enzymes.1 Everolimus is extensively metabolized in the liver via CYP450 3A4 (CYP3A4).2,3 Through induction of the 3A4 enzyme, phenobarbital is expected to increase the metabolism and elimination of everolimus, although an interaction between these 2 drugs is expected to occur.1

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polymorphism, this information is not readily available.

In patients with renal-cell carcinoma who require co-administration of everolimus with strong CYP3A4 inducers, the everolimus dose may be increased in 5-mg increments, from 10 mg to 20 mg daily, without monitoring of serum trough levels. This recommendation, however, is based on predictive models and not on clinical data.2,3

Although routine monitoring of everolimus levels is not recommended in the treatment of patients with renal-cell carcinoma, monitoring may be considered when everolimus is used in conjunction with agents that may significantly alter the drug’s pharmacokinetics.

Currently, the dosing for everolimus for the treatment for renal-cell carcinoma is standard, without the recommendation of monitoring serum trough levels for efficacy. However, for other indications, such as liver transplantation, renal transplantation, heart transplantation, and subependymal giant-cell astrocytoma, serum trough levels of everolimus are monitored for efficacy, with goal ranges relative to the specific indication (typically 3-15 ng/mL).2,8

Although routine monitoring of everolimus levels is not recommended in the treatment of patients with renal-cell carcinoma,9 monitoring may be considered when everolimus is used in conjunction with agents that may significantly alter the drug’s pharmacokinetics. A prudent approach may be to increase the drug’s dose in 5-mg increments, according to the manufacturer’s recommendations,2 and ensure that the trough level is at least detectable.

To our best knowledge, this is the first case describing the probable drug interaction between everolimus and the potent CYP3A4 enzyme inducer, phenobarbital.

Conclusion

Therapy with everolimus requires close supervision. Avoiding concomitant use of potent CYP3A4 inducers is prudent. When significant drug interactions with potent CYP3A4 inducers cannot be avoided, a dose increase in everolimus may be warranted, and sampling of trough levels may be considered.

Author Disclosure Statement

Dr Metayer and Dr Rozov have no conflicts of interest to report.

References

2. Afinitor/Afinitor Disperz (everolimus/everolimus tablets for oral suspension) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; April 2018.