

**Lamivudine and Hepatitis B Reactivation**

**TO THE EDITOR:** We read with great interest the systematic review by Loomba and colleagues (1) for chemotherapy-induced hepatitis B virus (HBV) reactivation in patients with cancer who tested positive for HBV surface antigen. However, some of the information quoted in the article needs clarification.

In Table 1 of the article, regarding the use of corticosteroids as an important risk factor for chemotherapy-induced HBV reactivation (2), our study (3) and the study by Lau and colleagues (4) were mistakenly categorized as either “not reported” or “not using corticosteroids.” In fact, both studies enrolled patients with lymphoma, and corticosteroids were an integral component of most standard chemotherapy for lymphoma. Therefore, in both studies, corticosteroids were used to treat participants.

In Table 1 of the article, our study was categorized as a prospective cohort study with historical control groups. In fact, our study was a randomized, controlled clinical trial (ClinicalTrials.gov identifier: NCT00201318). We enrolled patients with newly diagnosed non-Hodgkin lymphoma and randomly assigned them to either prophylactic lamivudine during chemotherapy or therapeutic lamivudine on hepatitis flare. The incidence of both HBV reactivation and HBV-related hepatitis flare were significantly reduced by prophylactic lamivudine. Our article also indicated that therapeutic lamivudine did not reduce the severity of HBV-related hepatitis or change the pattern of HBV reactivation.

In the Discussion section of their article, Loomba and colleagues mentioned that we proposed a duration of prophylactic lamivudine of at least 8 months after completion of chemotherapy. Although our study indicated that HBV reactivation may occur more than 6 months after completion of chemotherapy, we did not recommend a specific duration of prophylactic lamivudine. The optimal duration of prophylactic lamivudine is still unknown. Most previous studies continued lamivudine prophylaxis for 1 to 3 months after completion of chemotherapy, and the current guidelines by the American Association for the Study of Liver Diseases recommended prophylactic lamivudine for at least 6 months after completion of chemotherapy on the basis of expert consensus (5). The potential benefit of longer-term antiviral therapy must be judged against the risk for inducing viral mutants and drug resistance. Further clinical trials to determine the optimal duration and agents of antiviral therapy are definitely warranted.

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**Potential Financial Conflicts of Interest:** None disclosed.

**References**


**IN RESPONSE:** We thank Dr. Hsu and colleagues for their comments on our meta-analysis. We agree that corticosteroids play an important role in chemotherapy-induced HBV reactivation, which is why we listed corticosteroid use in a dedicated column in Table 1 of our article. Unfortunately, as apparent from the adjacent chemotherapy column showing administration of CHOP (cyclophosphamide, Adriamycin, Oncovin [vincristine], and prednisone), patients in the studies by Lau and colleagues (1) and Hsu and associates (2) were both erroneously labeled as not receiving corticosteroids and not reporting corticosteroid use, respectively. We also acknowledge that, instead of being listed as a randomized clinical trial with therapeutic (deferred) lamivudine control groups, the study by Hsu and colleagues (2) was inadvertently classified as prospective with historical control groups in our Table 1 and figures. It should be noted, however, that we quoted the meeting abstract of the study published by the authors (2) and not the article they reference as being quoted (3). Their full manuscript with the cited clinical trial identifier was not published until after the acceptance of our meta-analysis. In addition, the corresponding authors of all the published studies and abstracts included in our meta-analysis were contacted by e-mail for further clarifications but did not respond. The meeting abstract title did not mention that the study was a randomized, controlled study (2), and the title was reworded only later when published in its entirety (3). Because our research synthesis did not pool data from various studies, the apparent misclassification of this study has no effect on the conclusions.

The statement in our Discussion section about the duration of prophylactic lamivudine was based on a direct quote from the Conclusion section of the abstract by Hsu and colleagues (2): “The duration of lamivudine prophylaxis, which can reduce the incidence and severity of HBV reactivation and hepatitis during chemotherapy, may have to be no less than 8 months after completion of chemotherapy.” That is, in the source that we cited, the authors did indeed recommend a specific duration (at least 8 months) of prophylactic lamivudine after discontinuation of chemotherapy (2).
Potential Financial Conflicts of Interest: None disclosed.

References

Clarifying the Principles of Cost-Effectiveness Analyses

TO THE EDITOR: In their recent editorial (1), which accompanies the cost-effectiveness analysis by Pletcher and colleagues (2), Wong and associates explain the rationale supporting cost-effectiveness analysis as a guiding principle in the allocation of health care resources. Unfortunately, I found the editorial’s example of this principle unclear and thus find it difficult to apply the method to other questions of health care–related resource allocation.

Using the incremental cost-effectiveness ratio estimates provided by Pletcher and colleagues, Wong and associates project the gain in quality-adjusted life-years expected if $1 million is allocated to primary prevention under different statin scenarios in a hypothetical cohort of 154 persons. However, without additional information on the distribution of heart disease and the associated allocation of costs to prevention or treatment at baseline in that cohort, I cannot recreate their calculation of the point at which total cost exceeds the available budget of $1 million. This is not to take issue with the important conclusions of the editorial—that a trade-off exists between prevention and treatment, and a fixed budget will constrain adoption of less efficient strategies. However, at least for some readers, a clearer explanation of the calculation could help further advance this argument.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Cost-effectiveness analysis enables policymakers to maximize outcomes without exceeding available resources by determining either the greatest possible benefit for a given resource or the lowest cost for a given benefit. To illustrate, Pletcher and colleagues (1) estimated average annual discounted health care costs of $897.64 billion (Table 2) for 138.6 million men and women age 35 to 85 years at baseline, yielding an average cost of $6477 per treated or untreated person. The next most expensive policy options were treating persons with 10-year coronary heart disease (CHD) risk greater than 15% or adhering to Adult Treatment Panel III (ATP III) guidelines, which would cost $6487 or $6503 per person, respectively. So for all 3 of these policies, about 154 individuals could be covered per year for statin primary prevention with an annual budget of $1 million.

These alternative policies affect who receives treatment and where health dollars are consumed. Changing policies would increase the proportion of the population receiving statins from 35% to 42% and would result in up to 33% of persons older than 65 years starting statin therapy. By increasing the proportion of patients receiving statins, drug-related costs increase by $2 to $6 billion, but $1 to $3 billion less would be spent on CHD-related complications, such as hospitalizations and procedures. Because annual deaths from heart disease would decrease, annual non-CHD health expenditures would increase by $270 to $560 million annually.

Put simply, divide $1 million by each incremental cost-effectiveness ratio. Spending $1 million increases population health by 27 years by treating persons with 10-year CHD risk greater than 15% and by 22 years in patients treated according to ATP III guidelines. Focusing on treatment of persons with 10-year CHD risk greater than 15% is a more efficient use of resources, so it should be preferred. Spending $1 million on hemodialysis, with its cost-effectiveness ratio of $60 000 per quality-adjusted life-year gained (2), yields 17 years, so relative to hemodialysis, adhering to ATP III guidelines provides similar health value for its costs.

Can the United States “raise health care’s quality and lower its costs” (3)? Similar to its financial system, the U.S. health care system is complex and adaptive, with individual agents acting independently and not predictably (4). In such a system, instead of overspecifying a solution, targeting a few simple, flexible goals may enable the complex interacting parts of our health delivery and research enterprise to self-adjust and arrive at creative solutions (5, 6) involving such issues as coverage, malpractice, and payment reform for health policy to align economic incentives for improving health and move from a fee-for-service system (in which more is presumed to be better) to a system that provides quality care at a sustainable and affordable cost.

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Potential Financial Conflicts of Interest: Dr. Wong is a medical editor for the Foundation for Informed Medical Decision Making.

References
CLINICAL OBSERVATION

Posaconazole-Induced Topiramate Toxicity

Background: Posaconazole is an azole antifungal agent that is excreted primarily unchanged in the feces (77%). It is an inhibitor of CYP450 3A4 but is predominantly metabolized by glucuronidation and thus believed to have a narrow drug interaction profile compared with other azoles (1). Topiramate is a novel anticonvulsant that is said to be 55% to 97% excreted unchanged by the kidneys, with the remainder undergoing hepatic metabolism via CYP450. Symptoms of topiramate toxicity include drowsiness, lethargy, dizziness, vertigo, agitation, and confusion (2).

Objective: To report a case of suspected posaconazole-induced topiramate toxicity.

Case Report: A 48-year-old white man underwent partial pneumonectomy for invasive aspergilloma after radiation therapy. He was treated with intravenous conventional amphoterin C perioperatively and started posaconazole treatment at discharge.

Two weeks after discharge, the patient was rehospitalized for 10 days of progressive stupor, daytime somnolence, anorexia, decreased oral intake, and weight loss. The patient was observed by his mother to sleep approximately 6 hours during the day, drink only water, and be minimally responsive and interactive. She described his state as “catatonic.”

Medical history consisted of long-standing epilepsy stabilized with valproate and topiramate treatment and hemiglossectomy for lingual squamous cell carcinoma. His medications on admission were topiramate, 100 mg twice daily, and valproate, 700 mg twice daily. Posaconazole, 200 mg 4 times daily, had been discontinued 2 days before admission after a discussion with us.

The differential diagnosis for the patient’s stupor included sepsis, intracranial abnormality, and an adverse drug reaction. Topiramate toxicity secondary to a drug interaction with posaconazole was suspected. Posaconazole was replaced with intravenous amphotericin B perioperatively and started posaconazole treatment while awaiting therapeutic drug monitoring. The patient’s stupor and appetite gradually improved over 10 days, and he was discharged 3 weeks after admission.

Topiramate plasma levels on admission were grossly elevated for the given dose of 100 mg twice daily, at 27.34 μmol/L. Although correlation among plasma topiramate levels, efficacy, and toxicity has not been defined, pharmacokinetic modeling suggests that a peak plasma concentration of 5 μmol/L might be expected for a 100-mg dose (3). Repeated investigations 11 days after cessation of posaconazole revealed a topiramate level of 11.51 μmol/L, which coincided with partial resolution of the obtundation. Valproate levels remained in the therapeutic range throughout the admission. The patient began treatment with voriconazole, with careful monitoring of valproate, topiramate, and voriconazole levels. The patient completed the course of antifungal therapy without further complications.

Discussion: We postulate that posaconazole inhibition of CYP450 3A4 caused the patient’s elevated topiramate levels. Although the literature reports that topiramate is predominantly excreted unchanged in urine, hepatic metabolism is known to be as high as 50% with coadministration of such enzyme inducers as carbamazepine and phenytoin (4). Therefore, CYP450 3A4 is a common enzymatic pathway for posaconazole and topiramate metabolism. Competition for p-glycoprotein by posaconazole may also explain the elevated levels of topiramate, because both drugs have been identified as substrates for this transport protein (5). Plasma protein binding interactions or a renal mechanism as an explanation for the interaction are considered unlikely.

An alternative explanation would be encephalopathy induced by valproate secondary to increased topiramate levels. Case reports suggest the addition of topiramate to patients who are stable during valproate treatment can precipitate hyperammonemic encephalopathy (6). Serum ammonia analysis was not performed in this case; however, the patient had been stable while using this drug regimen for many years, with no evidence of encephalopathy.

Conclusion: Posaconazole may cause a clinically significant increase in topiramate levels. Further pharmacokinetic analysis of the interaction between posaconazole and topiramate is warranted to confirm the interaction and elucidate the precise mechanism.

Potential Financial Conflicts of Interest: None disclosed.

References

CORRECTIONS

Correction: Evolving Concepts in Potassium Homeostasis and Hypokalemia

The glossary of a recent article on potassium homeostasis and hypokalemia (1) had errors in the definitions of 2 terms, which should read as follows:

- **Na,K-ATPase**: Plasma membrane protein that pumps 3 sodium ions out of the cell and 2 potassium ions into the cell.
- **H,K-ATPase**: Plasma membrane protein that pumps 1 hydrogen ion out of the cell and 1 potassium ion into the cell.
Correction: Glycemic Control in Type 2 Diabetes

In the recent article on glycemic control in type 2 diabetes by Montori and Fernández-Balsells (1), the figure contained several incorrect numbers of patients in the intensive glycemic control (IGC) and conventional glycemic control (CGC) groups. The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study had 498 all-cause mortality events in the IGC group. The VADT (Veterans Affairs Diabetes Trial) had 40 and 33 cardiovascular mortality events in the IGC group and CGC group, respectively. For neuropathy, the VADT had 202 events in the ICG group and 218 events in the CGC group, and the correct relative risk is 0.93 (95% CI, 0.79 to 1.10). The correct relative risks for severe hypoglycemia in VADT and ADVANCE are 2.74 (CI, 1.80 to 4.17) and 1.85 (1.42 to 2.42), respectively. Denominators in the ICG and CGC groups for each study are 5128 and 5123 for ACCORD (Action to Control Cardiovascular Risk in Diabetes), 892 and 899 for VADT, 5571 and 5569 for ADVANCE, 2729 and 1138 for UKPDS(a) (United Kingdom Prospective Diabetes Study), 342 and 411 for UKPDS(b), and 1293 and 411 for UKPDS(c). Please note that these errors do not affect the article’s conclusions. The online version of the figure has been corrected.

Reference