Concomitant Use of Carbamazepine and Rifampin in a Patient With *Mycobacterium avium* Complex and Seizure Disorder

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Abstract

Objectives. To report a probable interaction between rifampin and carbamazepine, likely leading to a seizure, and to review conflicting reports regarding this interaction. **Case Summary.** A 55-year-old female was treated with carbamazepine 200 mg 3 times daily for grand mal seizures, with excellent control. A 6-hour postdose carbamazepine concentration was 10.7 µg/mL (therapeutic range = 4–10 µg/mL). After she was diagnosed with pulmonary *Mycobacterium avium* complex, she received rifampin 300 mg twice daily, ethambutol 800 mg daily, and clarithromycin 500 mg twice daily. At first clinic visit, rifampin was changed to 600 mg daily, and clarithromycin was replaced with azithromycin 250 mg daily. A 4-hour postdose carbamazepine concentration was 7.1 µg/mL. Two weeks later, the patient experienced a seizure (no carbamazepine concentration reported at that time), but admitted to missing doses of carbamazepine. After experiencing 2 more seizures, the patient stopped taking rifampin. Subsequently, the carbamazepine dose was increased to 400 mg twice daily and rifampin was restarted at 600 mg daily. Two follow-up peak carbamazepine concentrations were 4.7 µg/mL and 4.4 µg/mL, with no reported seizures. No additional factors were identified as potential causes of the seizures or the lower carbamazepine concentrations. A Drug Interaction Probability Scale score of 6 indicates a probable interaction. **Discussion.** Conflicting reports exist regarding the effect of rifampin on carbamazepine concentrations, likely reflecting rifampin's ability to display time-dependent, mixed effects on transporters and cytochrome P450 enzymes. **Conclusions.** Our case report describes a patient who experienced seizures after the addition of rifampin to her regimen, followed by lower peak concentrations of carbamazepine. Therapeutic drug monitoring in patients receiving both rifampin and carbamazepine is recommended to help clinicians optimize drug therapy.

Keywords

rifampin, carbamazepine, drug interaction, therapeutic drug monitoring, *Mycobacterium avium* complex

The concurrent use of rifampin and carbamazepine generally is not recommended due to rifampin's potential to reduce carbamazepine concentrations through CYP3A4 induction. However, clinical data regarding the interaction of rifampin with carbamazepine are sparse. Most previous reports of anti-mycobacterial drugs used with carbamazepine have indicated an *increase* in carbamazepine concentrations, stemming from the use of isoniazid, sometimes co-administered with rifampin.^{1–3} One report shows a *decrease* in carbamazepine concentrations in a patient taking isoniazid and rifampin.⁴ Here, we report a probable interaction of rifampin with carbamazepine in a patient not receiving isoniazid and a possible explanation for the conflicting reports.

Case Report

The patient was a 55-year-old woman with a past history of grand mal seizures and chronic obstructive pulmonary disease (COPD). She was referred to our nontuberculous

mycobacterial (NTM) disease clinic for treatment of pulmonary *Mycobacterium avium* complex (pMAC) infection. Her seizure disorder had been adequately controlled with carbamazepine (Tegretol XR) 200 mg 3 times daily, and her COPD controlled with fluticasone/salmeterol (Advair) 500 to 50 µg/actuation 1 puff 4 times daily, plus tiotropium (Spiriva) 1 puff daily. Several months prior to her initial visit to our clinic, the patient had begun treatment of pMAC with ethambutol 800 mg daily, clarithromycin 500 mg twice daily, and rifampin 300 mg twice daily (the latter being an unconventional dose and frequency). A 6-hour postdose

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Figure 1. Patient timeline.

Abbreviations: RIF, rifampin; EMB, ethambutol; CLARI, clarithromycin; AZI, azithromycin; CARB, carbamazepine; pMAC, pulmonary *Mycobacterium avium* complex.

carbamazepine concentration prior to adding these 3 drugs was 10.7 $\mu\text{g/mL}$ (normal range = 4–10 $\mu\text{g/mL}$). The patient reported no seizures while on this regimen; no carbamazepine concentrations were available after the 3 pMAC drugs were started. However, pMAC treatment was stopped by the patient for financial reasons after 2 months (see Figure 1 for patient timeline).

On exam, she weighed 62 kg with a body mass index of 21.30 kg/m^2 . Vital signs and the remainder of her examination were unremarkable; liver function tests (LFTs) were within normal limits. On computed tomography of the chest, she had a thick-walled cavitory lesion in the left upper lobe. Emphysematous changes were seen throughout both lungs. A culture was positive for *Mycobacterium intracellulare*. A 4-hour postdose carbamazepine concentration at this clinic visit was 7.1 $\mu\text{g/mL}$. Following her initial visit in our specialty clinic, treatment for pMAC was reinitiated with azithromycin 250 mg daily, ethambutol 1000 mg daily, and rifampin 600 mg daily, with orders for monitoring carbamazepine concentrations. Azithromycin was substituted for clarithromycin to avoid the well-known interaction between rifampin and clarithromycin, which converts most of the latter drug into 14-hydroxy clarithromycin, which lacks activity against pMAC.^{5,6} Approximately 2 weeks later, the patient experienced a seizure, although she admitted to “missing a dose or two of Tegretol” during this time. She was counseled on the importance of adherence, and repeat orders were given for carbamazepine concentrations. Following 2 more reported seizures, she stopped rifampin because she thought “that rifampin causes seizures.” At her return clinic visit, we recommended she continue the pMAC regimen, and we educated her about the probable interaction of rifampin and carbamazepine. We increased the dose of carbamazepine (Tegretol XR) from 200 mg 3 times daily (600 mg total) to 400 mg twice daily (800 mg total), with monitoring of carbamazepine concentrations. At the 6-week follow-up, she reported adherence to her

revised regimen and no further seizures. No concentration of carbamazepine was reported to us at that time, although her primary care physician reported that it was within the normal range. At subsequent, consecutive 6-week follow-up visits, the concentrations of carbamazepine were 4.7 $\mu\text{g/mL}$ (~4 hours postdose) and 4.4 $\mu\text{g/mL}$ (~4 hours postdose). She reported no seizures during this time.

Discussion

Our review of the literature showed that isoniazid increases carbamazepine concentrations through inhibition of CYP3A4.^{1–3} Fleenor et al reported a patient’s carbamazepine concentrations increased when co-administered with both isoniazid and rifampin. Prior sequential values of carbamazepine measured 8.5 $\mu\text{g/mL}$ and 9.5 $\mu\text{g/mL}$. Following the addition of isoniazid and rifampin, the carbamazepine concentration was 16.9 $\mu\text{g/mL}$.¹ Rifampin was added 3 days after isoniazid, and the authors suggested that it appeared to have “augmented the isoniazid effect” within 24 hours, producing side effects such as nausea/vomiting, confusion, and nystagmus. Removal of isoniazid and rifampin resulted in a resolution of symptoms within 24 hours. In contrast, a case report by Zolezzi describes a reduction in carbamazepine concentrations following administration of both isoniazid and rifampin.⁴ The latter case does not report carbamazepine concentrations prior to antimycobacterial administration but states the patient was within the normal range. Two weeks following the addition of isoniazid and rifampin, the patient’s carbamazepine concentration was 3.1 $\mu\text{g/mL}$, and steadily declined each week thereafter: 2.8, 2.5, and 2.3 $\mu\text{g/mL}$. Five days after discontinuing isoniazid and rifampin, the carbamazepine concentration was within the normal range (4.9 $\mu\text{g/mL}$), and 2 months after discontinuing isoniazid and rifampin, the carbamazepine concentration remained within the normal range (4.6 $\mu\text{g/mL}$).

The 2 case reports reflect different durations of treatment. Rifampin can display time-dependent mixed effects, at least with some other medications.^{7,8} Single doses of rifampin inhibit some organic anion transport proteins (OATPs) and p-glycoprotein (P-gp), while rifampin is a potent inducer of most CYP enzymes when administered chronically.⁹ For example, single doses of rifampin increases the concentration of atorvastatin via OATP1B1 inhibition, but chronic daily doses decrease concentrations via CYP3A4 induction.^{10,11} For our case, we do not know if rifampin acted as an inhibitor during the first few days of co-administration with carbamazepine, before induction became apparent. It is not known if carbamazepine is a substrate for an OATP or other transporters such as P-gp in humans, though recent in vitro and animal studies suggest it is not a P-gp substrate.^{12,13} Furthermore, prior to coming to our clinic, the patient also received clarithromycin, a potential inhibitor of CYP3A4. Thus, clarithromycin may have served the role described for isoniazid in the previous reports cited.

When faced with potential rifampin drug interactions, rifabutin is a possible substitute for rifampin. Rifabutin is approximately 40% as potent an inducer as rifampin.^{14,15} However, rifabutin also is a CYP3A4 substrate. Since carbamazepine is a CYP3A4 inducer, a complex bidirectional interaction would have been possible for our patient. For our case, the prior successful use of rifampin (along with clarithromycin) suggested that a balance could be struck for this patient. Our clinical experience suggests that many pMAC patients tolerate rifampin much better than rifabutin.¹⁶ Therefore, we chose rifampin, with a plan for close monitoring of the carbamazepine concentrations.

The complex nature of this case precludes assigning a definitive cause for her seizure. The DIPS (drug interaction probability scale) indicates a probable interaction (score of 6).¹⁷ The combination of noncompliance, change of macrolide from clarithromycin to azithromycin, and rifampin's inductive effect all may have played a role. Furthermore, rifampin had been dosed at 300 mg prior to coming to our clinic, but this still appears to be sufficient to fully induce CYP enzymes.⁹

In conclusion, if rifampin and carbamazepine must be used concomitantly, lower carbamazepine concentrations should be expected. In the absence of other CYP enzyme inhibitors, when steady-state rifampin induction is reached, decreased carbamazepine concentrations are likely, and carbamazepine dose increases may be required. Therapeutic drug monitoring (TDM) of carbamazepine (and consideration of TDM for the antimycobacterial drugs) should be undertaken to guide dosing. Finally, clinicians should emphasize the importance of adherence to drug regimens and TDM appointments.

Declaration of Conflicting Interests

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References

1. Fleenor ME, Harden JW, Curtis G. Interaction between carbamazepine and antituberculosis agents. *Chest*. 1991;99:1554.
2. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. *Br Med J (Clin Res Ed)*. 1982;285:261-262.
3. Wright JM, Stokes EF, Sweeney VP. Isoniazid-induced carbamazepine toxicity and vice versa: a double drug interaction. *N Engl J Med*. 1982;307:1325-1327. doi:10.1056/NEJM198211183072107.
4. Zolezzi M. Antituberculosis agents and carbamazepine. *Am J Psychiatry*. 2002;159:874.
5. Gelisse P, Hillaire-Buys D, Halaili E, et al. Carbamazepine and clarithromycin: a clinically relevant drug interaction. *Rev Neurol (Paris)*. 2007;163:1096-1099.
6. Wallace RJ Jr, Brown BA, Griffith DE, Girard W, Tanaka K. Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for *Mycobacterium avium-M. intracellulare* infection. *J Infect Dis*. 1995;171:747-750. doi:10.1093/infdis/171.3.747.
7. Reitman ML, Chu X, Cai X, et al. Rifampin's acute inhibitory and chronic inductive drug interactions: experimental and model-based approaches to drug-drug interaction trial design. *Clin Pharmacol Ther*. 2011;89:234-242. doi:10.1038/clpt.2010.271.
8. Lau YY, Okochi H, Huang Y, Benet LZ. Pharmacokinetics of atorvastatin and its hydroxy metabolites in rats and the effects of concomitant rifampicin single doses: relevance of first-pass effect from hepatic uptake transporters, and intestinal and hepatic metabolism. *Drug Metab Dispos*. 2006;34:1175-1181. doi:10.1124/dmd.105.009076.
9. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet*. 2003;42:819-850. doi:10.2165/00003088-200342090-00003.
10. Backman JT, Luurila H, Neuvonen M, Neuvonen PJ. Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther*. 2005;78:154-167. doi:10.1016/j.clpt.2005.04.007.
11. Lau YY, Huang Y, Frassetto L, Benet LZ. Effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. *Clin Pharmacol Ther*. 2007;81:194-204. doi:10.1038/sj.clpt.6100038.
12. Owen A, Pirmohamed M, Tetley JN, Morgan P, Chadwick D, Park BK. Carbamazepine is not a substrate for P-glycoprotein. *Br J Clin Pharmacol*. 2001;51:345-349. doi:10.1046/j.1365-2125.2001.01359.x.

13. Baltes S, Gastens AM, Fedrowitz M, Potschka H, Kaever V, Loscher W. Differences in the transport of the antiepileptic drugs phenytoin, levetiracetam and carbamazepine by human and mouse P-glycoprotein. *Neuropharmacology*. 2007;52:333-346. doi:10.1016/j.neuropharm.2006.07.038.
14. Li AP, Reith MK, Rasmussen A, et al. Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in cytochrome P450 induction potential of xenobiotics: evaluation of rifampin, rifapentine and rifabutin. *Chem Biol Interact*. 1997;107:17-30.
15. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis*. 1999;28:419-429. doi:10.1086/515174.
16. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367-416. doi:10.1164/rccm.200604-571ST.
17. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*. 2007;41:674-680. doi:10.1345/aph.1H423.