Warfarin-Rifampin Drug Interaction in a Pediatric Patient

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Rifampin has been documented to significantly attenuate the effect of warfarin in adult patients. No data have been presented on the use of rifampin and warfarin in a pediatric patient. We report an extreme case of increased warfarin metabolism in a pediatric patient who was concomitantly receiving rifampin, despite receiving other medications that significantly decrease warfarin metabolism. The inhibitory effect of rifampin on warfarin therapy may be amplified in pediatric patients.

ABBREVIATIONS INR, international normalized ratio

KEYWORDS INR; pediatric; rifampin; warfarin

J Pediatr Pharmacol Ther 2017;22(5):375–377

DOI: 10.5863/1551-6776-22.5.375

Background

Drug-drug interactions are numerous with warfarin therapy. Most of the reported interactions with warfarin consist of inhibition of warfarin metabolism, resulting in elevated international normalized ratio (INR) values and decreased warfarin dosing requirements. Rifampin, a potent inducer of CYP3A4, has been shown in adult patients to increase warfarin metabolism, necessitating increased warfarin dosing to achieve therapeutic INR values.¹ We report a unique case of a pediatric patient receiving concomitant rifampin-warfarin therapy leading to a dramatic increase in the dosing requirement, despite receiving other CYP3A4 enzyme-inhibiting medications.

Case Presentation

This study presents the case of a 10-kg, 20-month-old female with heterotaxy syndrome, right-ventricular–dominant atrioventricular canal defect, and a hypoplastic aortic arch had a history of aortic arch repair, pulmonary artery homograft, and Damus-Kaye-Stansel with bilateral bidirectional cavopulmonary anastomosis. As a result, the patient had a single-ventricle anatomy and physiology, with a common atrioventricular valve.

The patient was admitted to our institution because of atrioventricular valve regurgitation and subsequent heart failure. She underwent unsuccessful atrioventricular valve repair in order to decrease valvar regurgitation, leading to replacement with a 21-mm St Jude mechanical valve. The patient's postoperative course was remarkable for pulmonary hypertension and junctional ectopic tachycardia, treated with intravenous amiodarone.

The patient was initiated on anticoagulation with heparin for prevention of valve-associated thrombosis on postoperative day 2 but quickly transitioned fully to a maintenance dose of 1 mg daily of warfarin to maintain an INR in the range of 2.5 to 3.5. However, on

postoperative day 15, the patient exhibited strokelike symptoms and received a diagnosis of an ischemic right subcortical infarct (despite an INR value of 2.8 that day), and warfarin was transitioned back to unfractionated heparin therapy, given the concern for hemorrhagic transformation. The patient was evaluated for endocarditis; blood cultures were drawn and were subsequently positive for methicillin-resistant *Staphylococcus aureus*. The patient received a diagnosis of MRSA artificial valve endocarditis, and vancomycin, cefotaxime, gentamicin, and rifampin antimicrobial therapy was initiated. On postoperative day 18, the day after rifampin therapy was initiated, warfarin was reinitiated at 0.75 mg/day, a slightly lower dosage than the patient's last therapeutic dosage of 1 mg, targeting an INR range of 2.5 to 3.5. The patient was also receiving amiodarone and lansoprazole, each of which typically potentiates the warfarin effect. Patient hepatic enzymes were normal, at less than 2 times the upper limit of normal. The patient was receiving all medications and feeding via gastric tube.

The warfarin dosing requirements to achieve an INR value within the target range (2.5–3.5) increased from 1 mg/day to as large as 4 mg/day (from postoperative days 19 to 59), representing a 300% increase in dosage. After discontinuation of rifampin therapy (postoperative day 60), the patient had multiple instances of elevated INR values, leading to multiple held and decreased doses (Figure). At discharge, the patient had a therapeutic INR value on 1.5 mg of warfarin daily. At subsequent follow-up visits during the next 6 months, the patient required a dose of 0.5 mg alternating with 1 mg every other day to obtain an INR value of 2.5 to 3.5. A Drug Interaction Probability Scale calculation was conducted and resulted in a score of 7, which suggests a probable drug-drug interaction.²

Discussion

This is the first report of a warfarin-rifampin drug-drug

Figure. Time course of warfarin and rifampin use and INR response. The dose of warfarin (gray boxes) increased after initiation of rifampin (black box), and it decreased after discontinuation of rifampin. There is marked variability in INR values (black line), with elevations after discontinuation of rifampin until dose reduction. *INR, international normalized ratio.*

interaction in a pediatric patient. This report is notable not only for the age of the patient involved, but also for the dramatic increase in required warfarin dose despite other drug-drug interactions that would typically reduce the warfarin dosing requirement (amiodarone, lansoprazole). The observed time course was consistent with the reported time course of CYP3A4 induction by rifampin.

Previous reports in adult patients have described increased warfarin dosing in patients receiving concurrent rifampin therapy.^{1,3-5} However, the magnitude by which the dose requirements increased in our patient was significantly greater than those previously reported. The literature has previously described increases of 15% to 233% in weekly dose requirements in patients on concomitant warfarin and rifampin therapy.^{1,3,4} Our patient had a 300% increase in dose requirement.

The lack of an acceptable liquid formulation or compounded suspension of warfarin may have contributed to this apparently large increase in dosing requirement in our patient. The severity of this drug interaction was most likely to be due to the inability to titrate very small doses of warfarin in a pediatric patient, and unlikely to be due to physiologic factors, such as maturity of enzymes. The patient was nearly 2 years of age, at which point enzyme maturation would be nearly, if not completely, finished.⁶ In this patient case, warfarin was administered as crushed tablets in the smallest obtain-

able increment of 0.25 mg. Although recommended changes in dose to titrate to a therapeutic INR value are in the range of 10% to 20%, in pediatric patients the ability to make such fine, incremental changes is limited by commercially available tablet sizes that are relatively large in comparison with typical pediatric dosing requirements.⁷ Any dose adjustment thus tends to be relatively larger for a pediatric patient. Prior to the initiation of rifampin therapy, the patient had variable INR values, with significant changes in dosage. This variation continued after discontinuation of rifampin. This patient highlights the difficulty of warfarin management in very young patients.

It is also worth noting that common drug-drug interactions typically resulting in decreases in warfarin dose did not fully counteract the impact of rifampin. Amiodarone and lansoprazole are well documented to inhibit warfarin metabolism and decrease warfarin dose requirements.⁸⁻¹⁰ The patient presented did not have pharmacogenetic information, and future directions include the use of pharmacogenetic information to potentially manage or prevent this type of drug-drug interaction. We are hesitant to prescribe specific dosing practices in this patient case, because this interaction in a pediatric patient is rare and should be managed on a case-by-case basis. However, the clinician should be cognizant that a more aggressive approach to titration

is likely warranted when encountering this drug-drug interaction. This is important for clinicians to appreciate during the management of patients receiving warfarin and rifampin.

Conclusion

Pediatric patients receiving rifampin are at risk for an attenuated response to warfarin, potentially greater than that reported in adult patients. This drug interaction may occur despite concomitant use of medications known to potentiate the effect of warfarin. This report informs clinicians as to a potentially significant warfarin-rifampin drug interaction in pediatric patients.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all data and take responsibility for the integrity and accuracy of the data analysis.

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