

## CASE REPORT

# Interaction between Warfarin and Apple Juice

May Choi, Marcy Mintz, and Duane Bates

## INTRODUCTION

For decades, warfarin has been the primary anticoagulant for the primary and secondary prevention of venous and arterial thromboembolic events. There is an extensive amount of literature that has contributed to the understanding of the complex pharmacokinetics and pharmacodynamics of warfarin, its interactions with drugs and other compounds, its antithrombotic effects, and the risks associated with its use. To the authors' knowledge, however, there have been no case reports of an interaction between apple juice and warfarin. The following case report describes elevation of the international normalized ratio (INR) after ingestion of at least 1 L of homemade apple juice daily for 2 weeks in a patient who was previously stable on warfarin for venous thromboembolism.

## CASE REPORT

A 69-year-old woman was referred to the emergency department by her family physician for supratherapeutic INR.\* The patient denied any minor or major bleeding, despite the critical INR. Her medical history included recurrent deep venous thrombosis requiring lifelong anticoagulation, left parasagittal meningioma, hypertension, obstructive sleep apnea requiring continuous positive airway pressure, achalasia, gastroesophageal reflux disease, chronic hip pain, depression, restless leg syndrome, smoking (5 cigarettes/day), and several remote surgeries. The patient denied any recent alcohol use, new stressors, or recent illnesses. Medications before admission were nicotine 7-mg patch daily, baclofen 10 mg 3 times daily, pantoprazole 40 mg twice daily, salbutamol inhaler 1 or 2 puffs q4h as needed, gabapentin 600 mg 4 times daily, spironolactone 25 mg daily, pramipexole 1 mg daily, zopiclone 7.5 mg at bedtime as needed, diltiazem CD 120 mg daily, quetiapine 75 mg at bedtime, and warfarin 3 mg daily. The patient denied use of other over-the-counter

\*The patient gave informed consent for publication of this case report.

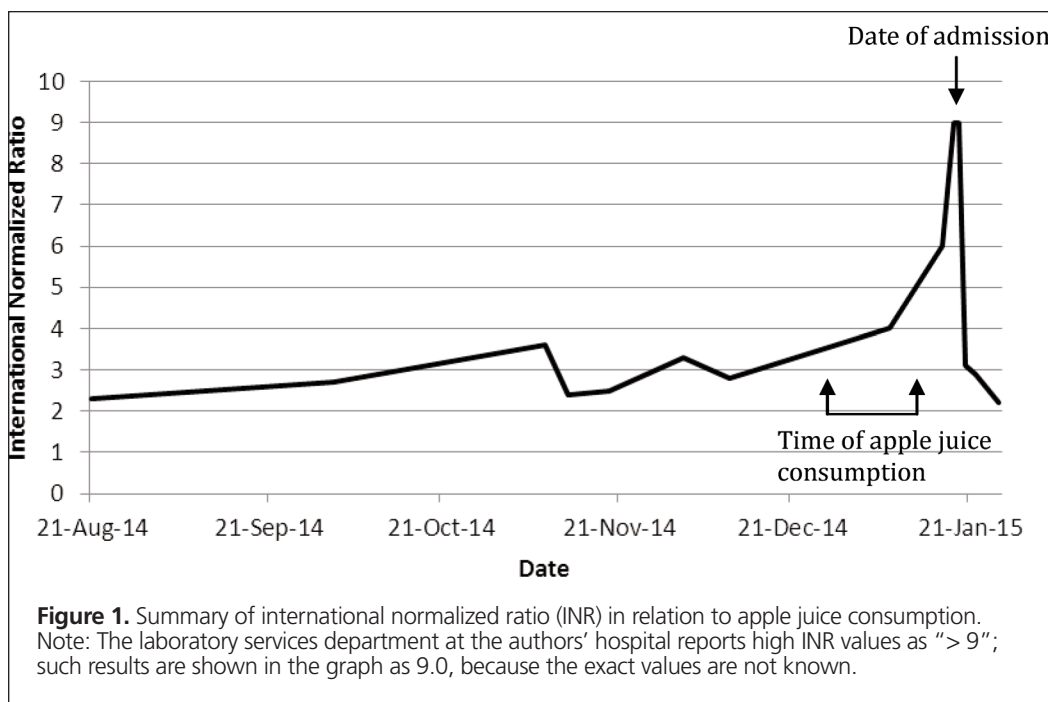
medications, herbal medications, natural health products, food supplements, or traditional medicines. She had good medication adherence. There were no recent changes to her medications, as confirmed by the patient and by refill dates on the prescription record provided within the electronic health record.

The INR had been relatively stable in the target range of 2–3 over the previous 5 months, with 2 isolated supratherapeutic readings ( $> 3$ ) in the 2 months before the current presentation. The only dietary change was consumption of at least 1 L of homemade pure apple juice daily during the 2 weeks before admission. During these 2 weeks, the INR had progressively increased, with measurements of 3.9, 4.0, 6.0, and finally above 9.0, with no change in warfarin dosing (Figure 1).

The results of a physical examination were unremarkable. Laboratory tests on admission included complete blood count, renal function tests, and measurement of albumin and liver enzymes, and all of the results were within normal range. The INR measured at the time of presentation was again greater than 9. Computed tomography (CT) of the head did not show any bleeding, and CT of the abdomen and pelvis showed no intra-abdominal or retroperitoneal bleeding. In the emergency department, the patient received 5 mg of oral vitamin K, and the warfarin was held. The next day, the patient's INR was 3.1, and she was discharged from hospital, with a recommendation for follow-up with the anticoagulation management clinic. The patient continued all previous home medications after discharge and was advised to discontinue drinking apple juice. At 6 days after discharge and cessation of apple juice, the INR was 2.2, and a month later it was 2.9 with a warfarin dose of 3 mg daily.

## DISCUSSION

To the authors' knowledge, this report is the first to propose a possible interaction between apple juice and warfarin. In this case, INR elevation was observed in a patient who was previously stable on warfarin after consumption of large amounts of apple juice over 2 weeks. The probability of a drug interaction was assessed using the Drug Interaction Probability Scale (DIPS),



a tool for evaluating the potential of a drug interaction in individual patients.<sup>1</sup> The DIPS is based on 10 questions relating to the potential drug interaction, with the results being used to estimate a probability score. A score greater than 8 suggests that a drug interaction is highly probable, whereas a score of 5–8 indicates a probable interaction, 2–4 a possible interaction, and less than 2 a doubtful interaction. In the case presented here, the DIPS score was 3, which suggested a possible interaction between warfarin and apple juice.<sup>1</sup>

A review of various drug interaction resources and databases<sup>2–6</sup> revealed no reports of an interaction between warfarin and apple juice. A literature search of Embase, Ovid MEDLINE, Google Scholar, Reactions Weekly, and International Pharmaceutical Abstracts from inception to June 2015 using the search terms “apple”, “apple juice” and “warfarin” yielded no evidence suggesting an interaction between warfarin and apple juice. To the authors' knowledge, there have been no in vitro or in vivo studies investigating the effects of apple juice on warfarin metabolism.

The mechanism by which apple juice interacts with warfarin may be similar to that of cranberry juice, as both of these juices contain flavonoids. In fact, apples are a significant source of flavonoids in the human diet.<sup>7</sup> In the United States, apples represent the largest source of phenolics, which are non-nutrient plant compounds, including flavonoids.<sup>7</sup> In fact, relative to other fruits, apples contain one of the largest amounts of total phenols, based on serving size and portion of free phenolics.<sup>8,9</sup> Flavonoids may inhibit membrane transporters, cytochrome (CYP) P450 enzymes, and P-glycoprotein.<sup>10</sup> Warfarin is extensively metabolized by hepatic cytochrome P450 microsomal enzymes.

Warfarin is a racemic mixture of 2 optical isomers, the *R* and *S* isomers, with the *S* isomer being 2 to 5 times more potent than the *R* isomer. *S*-Warfarin is metabolized principally by oxidation via the CYP2C9 isoenzyme and, to a lesser extent, the CYP3A4 isozyme. The less potent *R* enantiomer is also metabolized by oxidative metabolism, primarily by CYP1A2 and CYP3A4 and, to a lesser extent, by CYP2C19.<sup>11</sup> This suggests that the increase in INR may have been a result of apple juice inhibiting CYP P450 enzymes, which in turn reduced hepatic clearance of warfarin.

Some in vitro and in vivo studies have evaluated the interaction between cranberry and warfarin. Cranberry juice has been shown to inhibit CYP3A4 and CYP2C9.<sup>12</sup> Several studies have shown no change in warfarin pharmacokinetics with coadministration of cranberry juice, and most have demonstrated no change in INR.<sup>5,12</sup> However, many case reports have described an increase in INR and serious adverse reactions, including fatal hemorrhage, due to coadministration of cranberry with warfarin.<sup>5,12</sup> Consumption of large quantities of cranberry juice (1–2 L/day) or concentrate (1000 mg) for longer than 3–4 weeks may be correlated with altered INR values.<sup>12</sup> In vitro studies with cranberry juice have suggested that CYP3A4 and CYP2C9 inhibition is concentration-dependent.<sup>12</sup> The patient described here was consuming at least 1 L/day of homemade pure apple juice, which would be much more concentrated than commercially available apple juices and thus would have resulted in greater likelihood of inhibition of CYP enzymes, followed by reduced warfarin clearance and elevated INR.

Apple juice interacts with other medications via organic anion transporter polypeptides.<sup>5,6,13–15</sup> This mechanism is not relevant to the current case, as organic anion transporter polypep-

tides do not influence warfarin pharmacokinetics.<sup>5</sup> A review of the patient's medications before admission showed pantoprazole as the only medication that would inhibit organic anion transporters and result in inhibition of renal tubular secretion.<sup>5</sup> In this context, pantoprazole is classified as a weak inhibitor.<sup>5</sup> About 92% of warfarin is excreted in the urine as metabolites.<sup>3</sup> The metabolites of *R*-warfarin have some anticoagulant activity but considerably less than the parent compound.<sup>3</sup> A small double-blind, randomized, placebo-controlled, crossover study of pantoprazole and warfarin showed no clinically significant change in the pharmacokinetics and pharmacodynamics of *R*- and *S*-warfarin when coadministered with pantoprazole, and the combination was well tolerated.<sup>16</sup> Pantoprazole has low potential to interact with other medications, and there are no clinically significant metabolic interactions when pantoprazole is combined with warfarin.<sup>5,17</sup> However, the pantoprazole product monograph states that a few isolated cases of changes in INR have been reported during concomitant treatment with warfarin in the postmarketing period.<sup>18</sup> The patient had been receiving pantoprazole concurrently with warfarin for 3 years before the current admission. It is unlikely that a reduction in renal tubular secretion via inhibition of organic anion transporters caused the elevated INR, as warfarin does not require dosage adjustment in patients with renal dysfunction.<sup>3</sup>

## CONCLUSION

Warfarin is known to interact with many drugs and foods. Therefore, close monitoring of the INR is important to help prevent supratherapeutic or subtherapeutic levels of the drug, which can predispose the patient to excessive bleeding or thromboembolic events. To the authors' knowledge, this is the first case report of a potential interaction between warfarin and apple juice. In this case, INR became elevated in a patient who ingested excessive amounts of apple juice for 2 weeks. One limitation of this study is its reliance on subjective information from the patient, and although no confounding factors were identified, such factors cannot be ruled out. It is possible that apple interacts with warfarin in a manner similar to cranberry, through flavonoids. More studies are needed to assess this proposed interaction between warfarin and apple juice to understand the possible mechanism and clinical impact.

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