

# Warfarin Dosing after Initiation of Fenofibrate

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## INTRODUCTION

Anticoagulant therapy is central in the prevention and treatment of thromboembolic disease. Warfarin is currently the most commonly prescribed oral anticoagulant. Effective management of warfarin therapy is challenging, because of the drug's narrow therapeutic index and the multitude of factors influencing its anticoagulant effects. Drug interactions often result in changes to the patient's international normalized ratio (INR), which puts the patient at risk of bleeding or thrombosis.

Initiation of fenofibrate in patients whose warfarin therapy has been stabilized has been reported to increase INR values and put patients at risk of hemorrhage.<sup>1,3</sup> Trial-and-error dose decreases after observation of elevated INR have been described for patients receiving concurrent warfarin and fenofibrate therapy.<sup>1,3</sup> We report a case in which the anticipated effect of fenofibrate therapy on the patient's INR was managed proactively by aggressive reduction of the warfarin dose in the setting of therapeutic anticoagulation.

## CASE REPORT

A 28-year-old man who had undergone the Mustard procedure at age 2 to repair transposition of the great arteries had a history of congestive heart failure, dyslipidemia, and gout. The patient's warfarin therapy (INR target of 2.5) was initiated 15 months before initiation of fenofibrate, after discovery of a left ventricular thrombus. His other medications included colchicine 0.6 mg daily, allopurinol 300 mg daily, metoprolol 50 mg twice daily, ramipril 10 mg daily, and furosemide 40 mg daily.

The patient's INR had been stable (with warfarin 24–25 mg per week) for 22 weeks before initiation of the lipid-lowering therapy (Table 1). His heart function had also been stable. During routine follow-up with the

patient in the anticoagulant clinic, it was discovered that fenofibrate 200 mg daily had been initiated by the patient's physician the previous day. Before the initiation of fenofibrate, the patient's total cholesterol and triglyceride levels were elevated, at 5.98 and 4.15 mmol/L, respectively. The anticipated effect of fenofibrate on the INR was addressed by lowering the warfarin dose by 44%, even though the INR was within the therapeutic range (at 2.4). Assessment of the patient revealed no changes in diet, physical activity, alcohol intake, or nonadherence with warfarin therapy and no other changes in medications. One week after this aggressive dosage reduction, the patient's INR had fallen to 1.9. Subsequent adjustment of the warfarin dosage returned the patient's INR to the therapeutic range (Table 1). Therapeutic anticoagulation was subsequently achieved with warfarin 17 mg per week, an overall reduction of 32% in the warfarin dosage from what was being administered before initiation of fenofibrate. The patient did not experience any bleeding or clotting complications throughout this time period.

## DISCUSSION

Aggressive empiric reduction in warfarin dosage upon initiation of fenofibrate resulted in avoidance of the overanticoagulation that has previously been reported as a result of concurrent administration of the 2 medications.<sup>1,3</sup> This management strategy was implemented even though the INR, at 2.4, was within the therapeutic range. The initial reduction of 44% and the subsequent dosage adjustments (which resulted in a net decrease of 32%) avoided a significant increase in the patient's INR and therefore reduced the risk of bleeding complications.

Previous case reports of the interaction between these 2 drugs have revealed different strategies for managing the combination; in some cases, action has been taken only after the patient's INR became elevated (Table 2).<sup>1,3</sup> The case presented here is consistent with



**Table 1. Patient's History of Anticoagulation, Lipid-Lowering Therapy, and INR Results**

Date (2003)	Warfarin Dosage (mg/wk)	INR	New Warfarin Dosage (mg/wk)	Comments
January 30 to May 8	24–24.5	2.0–3.1	24–24.5	
May 8	24.5	3.1	24	Decreased weekly warfarin dose by 2%
May 23	24	2.1	24.5	Increased weekly warfarin dose by 2%
June 13	24.5	2.1	25	Increased weekly warfarin dose by 2%
July 8	25	2.4	14	Fenofibrate 200 mg daily initiated the day before (July 7, 2003); warfarin dose decreased by 44%; fenofibrate continued
July 14	14	1.9	16	Increased weekly warfarin dose by 14%
July 24	16	2.0	17	Increased weekly warfarin dose by 6.3%
August 6	17	2.6	17	No change in warfarin dose
August 12 to 16	Held			Warfarin therapy temporarily interrupted in preparation for routine cardiac catheterization
August 27	17	2.0	17.5	Increased weekly warfarin dose by 2.9%
September 25	17.5	3.1	17	Decreased weekly warfarin dose by 2.9%

INR = international normalized ratio.

**Table 2. Summary of Case Reports of Warfarin–Fenofibrate Interaction**

Source	Case Details	Empiric Warfarin Dose Decrease	Time to Reassessment of INR	INR	Management Strategy and Result	Authors' Recommendations for Management
Kim and Mancano <sup>1</sup>	71-year-old woman, warfarin dose stable at 23 mg/wk	None	15 days	6.7	Warfarin dose decreased by 37% to 41% to achieve therapeutic range	Monitor INR frequently; consider empiric 20% reduction in warfarin dosage
	80-year-old woman, warfarin dose stable at 20 mg/wk	0% after 1 week of fenofibrate therapy	3 weeks (2 weeks after decrease in warfarin dosage)	4.6	Warfarin dose decreased by 35% to achieve therapeutic range	
Aldridge and Ito <sup>2</sup>	79-year-old man, warfarin dose stable at 42 mg/wk	None	4 weeks	18	Fenofibrate discontinued; patient was not rechallenged	Monitor INR closely upon initiation of fenofibrate
Ascah et al. <sup>3</sup>	47-year-old man, warfarin dose stable at 12.5 mg alternating with 15 mg (about 96.25 mg/wk)	None	1 week	>8.5	Fenofibrate and warfarin discontinued; patient was rechallenged once INR had stabilized	Monitor INR closely upon initiation of fenofibrate
			13 days (after rechallenge of warfarin and fenofibrate)	5.0	NR restabilized with a warfarin dosage reduction of 27% to 29%	
	56-year-old man, condition stable on warfarin 35 mg/wk	None	10 days	5.6	Fenofibrate discontinued; patient was not rechallenged	

INR = international normalized ratio.

other reports, both in terms of the extent of dosage reduction required and the timing of onset of the interaction. The initial 10% reduction in warfarin dosage described by Kim and Mancano<sup>1</sup> was insufficient to maintain a therapeutic INR, and a total dosage decrease

of 35% was required to bring the INR back into the therapeutic range. These authors stated that an empiric 20% dosage reduction may be tried when fenofibrate is initiated; however, in a second case reported by the same authors, an overall dosage reduction of up to 41%



was required to bring the patient's INR back into the therapeutic range, which suggests that more aggressive reduction of the dose is necessary. Ascah and others<sup>3</sup> described a patient in whom warfarin dosage was reduced by 27% to 29%, similar to the overall 32% decrease required in the patient reported here.

As demonstrated by previous case reports,<sup>1,3</sup> the onset of the warfarin–fenofibrate interaction occurs 1 to 4 weeks after initiation of fenofibrate. This variability in onset may be an artifact of a delay in clinical assessment and limitations of practice rather than a reflection of the true timing of onset of elevated INR. Exaggerated anticoagulation effects may occur as early as 5–10 days after initiation of fenofibrate, and if warfarin dosage is not adjusted, patients are likely to present with a critical INR (above 5.0) within the first 2 weeks of combination therapy.<sup>1,3</sup> The case reported here is consistent with this pattern, in that the patient experienced only a small decrease in INR 1 week after a substantial decrease in warfarin dosage.

The mechanism of the interaction between fenofibrate and warfarin is not yet clearly understood. Fenofibrate is a moderate inhibitor of the cytochrome P450 enzyme system, which is responsible for warfarin metabolism, specifically the isoenzyme 2C9.<sup>1,4</sup> This inhibition is of particular interest in view of the possibility of genetic variants of CYP2C9, specifically the 2C9\*2 and 2C9\*3 polymorphisms. These variants have lower activity and have been associated with an increased risk of overanticoagulation, and many patients with these variants require lower doses of warfarin.<sup>4,5</sup> It is uncertain, however, if the variants affect the degree of the warfarin–fenofibrate interaction. The patient described here required lower maintenance doses of warfarin but has not been tested for the presence of genetic variants. It has been suggested that fenofibrate, like another fibric acid derivative, clofibrate, potentiates the effect of warfarin by affecting synthesis of coagulation factors, most likely by altering receptor synthesis.<sup>2,3</sup> A third mechanism for the interaction, though perhaps less significant, is fenofibrate's displacement of warfarin from its protein-binding sites, which may enhance the hypoprothrombinemic effects.<sup>6</sup> Other fibrates (gemfibrozil, bezafibrate) have also been reported to cause adverse drug reactions when administered with warfarin; thus, it is unlikely that switching to another fibrate would prevent the interaction.<sup>6</sup>

The case presented here was different from previously reported cases in that a supratherapeutic INR resulting from the warfarin–fenofibrate interaction was avoided by aggressive reduction of the warfarin dose in the presence of a therapeutic INR. It is important to assess each patient individually when attempting to

manage potential interactions of warfarin with other drugs. As each patient's response to warfarin therapy will vary, so will the degree of response to an interacting medication. Careful consideration must also be given to each patient's thrombotic and hemorrhagic risk profile before attempting any empiric dosage adjustments. In view of the published reports of warfarin dosage decreases of up to 41% to maintain a therapeutic INR after initiation of fenofibrate, as well as the authors' own experience, an empiric warfarin dosage reduction is recommended, along with more frequent monitoring of the INR in the first several weeks after the dosage change. Although the required empiric reductions may be more or less aggressive than what has previously been suggested in the literature, individual patient characteristics must be considered when determining the extent of the reduction.

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