

# Warfarin - Fenofibrate Interaction: Hospital Kuala Lumpur Experience

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## ABSTRACT

Case reports in western populations reported that fenofibrate enhances the anticoagulatory effect of warfarin. We are reporting ten cases of warfarin-fenofibrate interaction among Malaysian patients' cases that were managed at the anticoagulation clinic of Hospital Kuala Lumpur. Patients taking warfarin and micronized fenofibrate 145mg daily concurrently between the year 2014 to 2018 were identified in May 2018. Ten active patients were included, and the relevant data were retrieved retrospectively. All patients received warfarin for stroke prevention in atrial fibrillation (AF), with a target international normalised ratio (INR) of 2 to 3. No dose adjustment was done upon initiation of fenofibrate. Warfarin doses were adjusted to achieve the targeted range but fenofibrate was not discontinued. Eight patients had INR levels above the target range when INR being reassessed between 20 to 62 days after initiation of fenofibrate. Their weekly warfarin doses were between 17.5mg-46.5mg. Baseline INR ranged between 1.6 -3.1. Percentage of dose reduction ranged between 5%-60%. Four of the patients were on other concurrent interacting medications such as statin and levothyroxine. Only one patient, whose case was with an INR 3.1 before initiation of fenofibrate, required admission for hematoma (INR 12). Two patients had INR within the target range, and INR were assessed at 14 and 21 days after fenofibrate initiation. Their weekly warfarin doses were between 24.5mg and 26.5mg while baseline INR was 2.8 and 1.9 respectively. Interaction between fenofibrate and warfarin may increase INR among Malaysian patients, thus close monitoring of INR is warranted. Empirical warfarin dose reduction may be considered upon initiation of this drug combination for patients with AF. The next INR reassessment date should be arranged not later than three weeks after initiation of fenofibrate.

## INTRODUCTION

Warfarin has been the most commonly prescribed oral anticoagulant in the management of atrial fibrillation (AF), venous thromboembolism and valvular heart disease, despite the emergence of direct oral anticoagulants (DOACs). This has led to a high number of patients referred to anticoagulant clinics for warfarin therapy. The management of warfarin is challenging because the drug has a narrow therapeutic index and is accompanied by drug-drug, drug-food, and drug-disease interactions that may influence the anticoagulant effects. This may lead to a change in patients' international normalized ratio (INR) and poses a risk of bleeding or thrombosis.

In Malaysia, fenofibrate is prescribed for patients with mixed dyslipidaemia and hypertriglyceridemia as well as patients

with mild to moderate hypercholesterolemia who are statin intolerant [1]. According to the Malaysian Statistics on Medicines 2011 – 2014, there was an increasing trend of prescribing fenofibrates in the public sector [2]. The prevalence of dyslipidaemia in a patient with AF is 46.3% according to International AF Registry therefore co-administration of warfarin and fenofibrate by patients is becoming more common [3].

Fenofibrate had been reported to have major interaction with warfarin from case reports [4-6]. These case reports showed a significant increase in INR upon initiation of fenofibrate in patients whose warfarin therapy had been stabilized [4-6]. An increase in INR values will place the patients at higher risk of bleeding and/or hospitalization due to over-warfarinization. In order to address the issue, warfarin dose reduction or

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**Table I: Demographic data, baseline INR and weekly warfarin dose prior to initiation of fenofibrate of patients**

No	Age (years)	Gender	Ethnicity	INR before initiation of Fenofibrate (Pre)	INR within range (Pre)	Weekly Warfarin dose before initiation of Fenofibrate (mg)
1	68	Female	Indian	2.8	Yes	24.5
2	51	Male	Punjabi	2.9	Yes	46.5
3	67	Male	Chinese	1.6	No	27.0
4	59	Male	Indian	1.8	No	28.0
5	69	Male	Malay	1.9	No	26.5
6	55	Female	Indian	2.0	Yes	17.5
7	68	Female	Malay	1.8	No	39.5
8	46	Male	Malay	3.1	No	46.5
9	76	Female	Chinese	2.0	Yes	17.5
10	61	Male	Chinese	2.5	Yes	17.5

discontinuation of fenofibrate are the options that had been discussed [4]. Different values of total warfarin dose reduction upon initiation of fenofibrate had been concluded from these reports [4-6].

The mechanism of interaction between warfarin and fenofibrate is not clearly understood. One of the postulated mechanisms proposed is that the metabolism of either or both fenofibrate and (R)-enantiomer of warfarin, which are metabolized via CYP 3A4 enzymes will be delayed, hence leading to the reduction in the clearance of warfarin [7]. On the other hand, fenofibrate inhibits CYP 2C9, a cytochrome that metabolizes the (S)-enantiomer of warfarin, thereby reducing warfarin elimination [7]. Pea F and Furlanut M. (2001) suggested that the interaction is due to fenofibrate affecting the coagulation synthesis factor by altering receptor synthesis [8]. Lastly, it had been proposed that fenofibrate displaces warfarin from its protein-binding sites, hence enhancing the hypoprothrombinaemia effects [9].

Currently, limited published data is describing warfarin-fenofibrate interaction among the multiracial Malaysian population. Genetic variations in CYP2C9 lead to the variations in the response in warfarin metabolism [10]. Zhao et al showed that there are genetic variations of CYP2C9 in different Singapore ethnic groups, namely Malay, Chinese, and Indian, which are similar to the Malaysian population [11]. The details on the effect of warfarin-fenofibrate interaction in the Malaysian population are scarce. We report ten cases of warfarin-fenofibrate interaction among patients managed at Hospital Kuala Lumpur (HKL), Malaysia. This clinic is co-managed by medical officers and clinical/ trained pharmacists to optimise anticoagulation therapy.

## METHOD

The HKL Anticoagulation Registry was screened to identify patients prescribed with warfarin and fenofibrate concurrently, between 2014 and 2018. The relevant clinical information retrieved from the medical notes includes: demographic data, INR before and after initiation of fenofibrate, weekly warfarin

dose before and after initiation of fenofibrate, concurrent medications and incidences of bleeding. Incidences of bleeding include hematoma, gastrointestinal bleeding (GIB) and intracranial haemorrhage (ICH). Only incidences of bleeding that were documented by the medical practitioners in the case notes were considered. Results were limited to active adults of at least 18 years old who started on both warfarin and fenofibrate concurrently between 2014 and 2018.

Patients with missing needed data for the study, pregnant and lactating mothers were excluded. The study received approval from the National Medical Research Registration (NMRR-19-2171-48579).

## RESULT

Ten patients who fulfilled the inclusion criteria were identified during screening. All 10 patients received Micronized Fenofibrate 145mg (Lipantyl Penta® by Abbott) and a mixed brand of warfarin between 2014 and 2018. The 10 patients received warfarin for the indication of stroke prevention in AF, with a target INR of 2 to 3. Six of the patients were male. The demographic data, baseline INR, and weekly warfarin dose prior to initiation of fenofibrate of patients are presented in Table I. Patients ranged from 46- to 76-year-olds. The baseline INR ranged from 1.6 to 3.1 with the weekly doses of warfarin between 17.5 mg to 46.5 mg.

Details of the study data are presented in Table II. After initiation of fenofibrate, only two patients had their INR levels maintained within the target range while 8 patients had INR above the target range. No adjustment to the weekly warfarin dose was made upon initiation of fenofibrate in all 10 patients. Fenofibrate was not discontinued in all 10 patients.

For the 8 patients who had INR above the target range, their levels were reassessed between 20 to 62 days after initiation of fenofibrate. Weekly warfarin doses were between 17.5mg to 46.5mg with baseline INR between 1.6 and 3.1 upon initiation

Table II: Detail data of patients after initiation of Micronized Fenofibrate 145mg.

Patient No	Weekly Warfarin dose*(mg)	Time to reassessment of INR↓ (days)	INR ↓	INR within range (post)	Adjusted Weekly Warfarin dose ↓(post) (mg)	Percentage of weekly Warfarin dose reduction (%)	Remarks
1	24.5	21	2.8	Yes	24.5	No change	-
2	46.5	30	5.1	No	31.5	32	Gemfibrozil was substituted with fenofibrate Simvastatin was initiated on the same day.
3	27.0	57	3.6	No	25.0	7	Gemfibrozil was substituted with fenofibrate Simvastatin was substituted with atorvastatin.
4	28.0	62	3.4	No	26.5	5	-
5	26.5	14	2.7	Yes	26.5	No change	-
6	17.5	30	7.3	No	7.0	60	-
7	39.5	28	5.9	No	34.0	14	-
8	46.5	26	12.0	No	31.5	32	Gemfibrozil substituted with fenofibrate. Patient was warded due to hematoma & elevated INR (12.0) during the follow up in anticoagulation clinic.
9	17.5	39	4.65	No	11.5	34	
10	17.5	20	5.7	No	10.5	40	Levothyroxine dose was increased from 75 mcg once daily to 100 mcg once daily.

of fenofibrate. Warfarin doses were adjusted by the prescribers to achieve the target range. The percentages of weekly warfarin dose dosage adjustment to achieve the targeted ranged between 5% to 60%.

Four of the 8 patients were on other concurrent interacting medications such as statin and levothyroxine. Patient 2, patient 3, and patient 8 had fenofibrate initiated to substitute gemfibrozil. Patient 2 had simvastatin initiated on the same day as fenofibrate. This patient required 30% of the weekly warfarin dosage adjustment to achieve the targeted range. Patient 3 had simvastatin changed to atorvastatin on the day of fenofibrate initiation. This patient required 7% changes in the weekly warfarin dosage after initiation of fenofibrate to achieve the targeted INR range.

Patient 8 had an INR of 12 on the 26th days after the initiation of fenofibrate and required ward admission for hematoma. Fenofibrate was not stopped but the weekly warfarin dose was reduced by 32% to achieve the targeted INR range. The levothyroxine dose for patient 10 was increased from 75mcg to 100mcg on the day of initiation of fenofibrate.

Two patients who had INR within their targeted range were reassessed at 14 and 21 days after initiation of fenofibrate. Their weekly warfarin doses were between 24.5mg and 26.5mg while the baseline INR were 2.8 and 1.9 respectively.

## DISCUSSION

Eight patients were reported to have INR above the targeted range. This is similar to the previously published case reports [4-6], whereby warfarin – fenofibrate interaction led to an increase in INR for most of patients. The degree of changes varied with reported case reports and among the multi-ethnic patients in this case series. The overall weekly warfarin dose reduction from baseline was highest among the Indians (2 patients; 5% & 60%), followed by Chinese (3 patients, ranging between 7% to 40%) and the lowest in Malays (2 patients; 14% & 32%, respectively). It is unclear whether the genetic variations of CYP2C9 in different ethnicities contribute to the result.

Half of the patients required reduction of 30% or more of their weekly warfarin dose to achieve the target INR range. One patient (Patient 8) had reported hematoma after initiation of fenofibrate. The effect of fenofibrate in warfarin could potentially influence the INR of 12 and resulted in a hematoma. Previous studies had reported that the risk of major bleeding is high when INR is above 9 [12-13]. Our results were aligned with previous published case reports that required up to 41% warfarin dose reduction to maintain a therapeutic INR after initiation of fenofibrate [4].

Two of the patients had INR maintained within the target range 14 and 21 days after initiation of fenofibrate. The other eight patients' INR was above the target range of 20 to 62 days after

initiation of fenofibrate. The degree of INR elevation in these patients may be affected by the duration of INR reassessment after initiation of fenofibrate and concurrent interacting medications. Our results indicated that the potential for the onset of interaction between warfarin and fenofibrate occurs after 3 weeks.

Three patients had their lipid-lowering fibric acid derivatives switched from gemfibrozil to fenofibrate. Two of them (Patient 2 and Patient 8) required 32% weekly warfarin dose reduction to achieve the target INR range, patient 8 eventually required to be warded due to hematoma. Another patient (Patient 3) required only 7% weekly warfarin dose reduction, however the patient's simvastatin (Known to cause an increase in INR when used concomitantly with warfarin) had been switched to atorvastatin (No interaction with warfarin) on the same day as initiation of fenofibrate [14]. The lower magnitude of fenofibrate-warfarin interaction for patient 3 may be affected by the switching of statins. Further investigation is needed to review the contribution of these confounding factors towards the degree of interaction between warfarin and fenofibrate.

There are potential limitations to consider in our case series. The data were collected retrospectively without a control group. We were unable to assess the patient's adherence to the prescribed medication. Concurrent factors such as concurrent medications and a mixed brand of warfarin used by patients may have affected the outcome of the data.

## CONCLUSION

Empiric warfarin dosage reduction and close monitoring of patient's INR can be considered after initiation of fenofibrate based on authors' experience. Individual patient characteristics such as concurrent medications and patient's adherence to prescribed medications should be considered when determining the extent of empiric warfarin dosage reduction. The next INR reassessment date should be arranged not later than three weeks after initiation of fenofibrate.

Our data showed that the overall weekly warfarin dose reduction after initiation of fenofibrate varied among the multi-ethnic patients. The effect of different ethnicities on the degree of interaction between warfarin and fenofibrate requires further investigation.

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## CONFLICT OF INTEREST

There is no conflict of interest.

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