# Warfarin – Topical Salicylate Interactions : Case Reports

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## Summary

This paper deals with two patients on warfarin in whom the use of topical methylsalicylate preparations led to clinically significant bleeding problems. The first patient required fresh frozen plasma to tide over the crisis while the second patient recovered spontaneously on stopping the warfarin temporarily. The possible mechanisms by which salicylates potentiate the anticoagulant effect of warfarin are briefly outlined.

*Key Words:* Warfarin, Topical salicylates, Prothrombin time

## Introduction

Routinely, patients on warfarin are warned to be cautious with nonsteroidal antiinflammatory agents (NSAIDS), aspirin and related compounds. But, topical application of methylsalicylate preparations themselves may lead to clinically significant potentiation of warfarin anticoagulation as illustrated by the two patients presented here.

## Case Reports

### Case 1

A 25-year-old Malay male with chronic rheumatic heart disease since 1991 was admitted on 4th July 1994 with a three-day history of painful right calf swelling. He was on digoxin, frusemide, penicillin and potassium. In May 1994, his cardiologist started him on warfarin and at the time of admission, he was on warfarin 2 mg daily.

Initially, he was thought to have had developed deep venous thrombosis but further examination showed he had diffuse gum bleeding and a haemtoma on the right leg.

Routine haemoglobin, total white cell counts, platelets and liver function tests were normal. However, his international normalised ratio (INR) was high at 16. The INR on two previous occasions were in the range of 2.0 to 2.5.

Despite repeated questioning the patient maintained he was taking only the hospital medications. He had not changed the dosage of warfarin on his own. He was not on nonsteroidal antiinflammatory drugs (NSAIDS) or 'over the counter drugs' at the time of admission.

The patient's bleeding tendency was puzzling because his INR was previously normal. Blood salicylate level was determined and found to be 3.3 μg/dl.

On taking the patient's drug history again it was noted he was in the habit of massaging himself almost daily for the past several months with salicylate-containing liniment.

The patient required four units of fresh frozen plasma to tide over the present crisis. Two weeks later he was restarted on warfarin 2 mg daily with clear warning

that he should stop further application of any form of liniment. On subsequent follow-ups, he remains well with the INR being in the range of 2.0 to 2.5.

### Case 2

A 57-year-old retired teacher with chronic rheumatic heart disease underwent mitral valve replacement in 1983. Subsequently, she was on warfarin 2.5 mg daily with good compliance and regular Prothrombin Time (PT) monitoring. Her INR was previously in the range of 2.0 to 2.5.

She was seen in August 1994 with a two-week history of bleeding gums. Routine Hb, TWBC, Platelets and LFT were normal. But the INR was high at 3.5.

On direct questioning, the patient admitted to recent use of salicylate containing proprietary liniment but specifically denied oral preparations of salicylate-related compounds. Her serum salicylate was high at 8.8 µg/dl. Her bleeding gums subsided spontaneously after stopping warfarin for a week. She had been restarted on warfarin 2.5 mg daily with no further problems.

## Discussion

Several proprietary topical analgesic preparations with methylsalicylate as an active ingredient are freely available in the market. The use of these topical agents are generally thought to be innocuous. But, the need for patients on warfarin to be cautious in the use of topical salicylate preparations is clearly illustrated by the two patients presented here.

The positive blood levels of salicylate reflect the percutaneous absorption of topical methylsalicylate liniment. The absorbed salicylate in turn had augmented the anticoagulation effect of warfarin resulting in clinically significant bleeding tendencies in both the patients. There are several possible mechanisms for the adverse warfarin-topical salicylate interactions. Firstly, the salicylates effect on platelet functions itself increases the risk of haemmorrhage in patients on warfarin[1]. Secondly, high salicylate levels on their own can prolong INR by decreasing vitamin K dependent coagulation factors. Thirdly, salicylates can displace warfarin from protein binding sites resulting in increased free drug levels[2,3]. As has been observed by earlier workers, the potentiation of warfarin anticoagulation does not appear to be related to the blood salicylate level[2].

Thus the first patient had more severe bleeding than the second despite his salicylate level being much lower than the latter.

Routinely patients on warfarin are advised to be cautious with the use of NSAIDS. Similarly, we should counsel patients on anticoagulants on the potential hazards of topical methylsalicylate preparations.

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