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# Warfarin and Drug Interactions: Prescribing Vigilance

**Abstract:** A patient taking warfarin presented to the Oral Medicine Clinic at Liverpool University Dental Hospital, having been prescribed metronidazole and miconazole by his general dental practitioner (GDP) for his oral mucosal problem. He subsequently developed bruising on his torso following mild trauma. Having read the drug information leaflet provided with his metronidazole and miconazole, he noted the potential drug interactions between these and warfarin. He therefore stopped his warfarin. The details of this case are outlined, and the potential for significant drug interactions with warfarin are highlighted. The need for dental practitioners to be vigilant concerning drug interactions is emphasized, together with the importance of CPD in relation to drug prescribing.

**CPD/Clinical Relevance:** This case report, which is of relevance to all dental practitioners, highlights the importance of up-to-date medical and drug histories and the continuing awareness of potential drug interactions. In this case, patient intervention after checking drug information leaflets prevented serious consequences. The importance and potentially serious consequences of significant drug interactions needs to be understood.

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## Case report

A 68-year-old male attended the Oral Medicine Department of the Liverpool University Dental Hospital. The patient had been referred by his GDP regarding 'soreness of the gums and roof of mouth'.

The patient's complaint was of a sore mouth that made it difficult to eat and brush his teeth; this had been present for approximately three months and affected his palate, tongue and inside his cheeks. His GDP had prescribed metronidazole and miconazole for symptomatic relief of

his oral symptoms and then referred the patient to the Oral Medicine Department for specialist management.

During the initial consultation the patient also mentioned having bumped into the cooker three evenings ago which had left him with a large bruise on the right side of his stomach. The patient had read the information leaflet supplied with the miconazole and metronidazole and had seen that there was a potential interaction with his warfarin. He had therefore stopped taking his warfarin medication. The patient felt that his dentist would have wanted him to continue with the medications for his sore mouth and that it was the warfarin that needed to be discontinued.

The patient's medical history revealed that he had undergone a heart bypass in 2002 and was fitted with a pacemaker in 2009. The patient also suffered from asthma. His medication list included; ventolin inhaler, lansoprazole, candesartan, amlodine and warfarin (for which he carried a warning card). The patient's INR was monitored regularly by

a local anti-coagulation clinic. He was an ex-smoker, having given up cigarettes 30 years earlier, and he consumed around 16 units of alcohol per week.

On examination, the patient had a large bruise on his right torso (Figure 1). Intra-orally the buccal mucosae were erythematous with faint white striations present. There was also evidence of occlusal trauma. There were white striations and erosions on the mucosa of the hard palate, extending onto the attached gingivae (Figure 2). Clinically, the appearance was of erosive lichen planus with desquamative gingivitis.

An urgent INR blood test was arranged to check the patient's INR, as he had stopped his warfarin medication three days previously. This was reported as 5.9 (normal therapeutic range would be less than 4). An appointment was made with the patient's anticoagulant clinic for the next day, so that his warfarin could be appropriately re-started.

A topical steroid/antibiotic mouthrinse (triamcinolone with 2%

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aureomycin) was prescribed for the oral lesions, together with nystatin suspension. A biopsy appointment was arranged to confirm the diagnosis of oral lichen planus. A pre-operative INR was requested, in accordance with national guidelines<sup>1</sup> and this was recorded as 2.3 pre-operatively. An incisional biopsy from the palatal mucosa was taken under local anaesthetic. This confirmed a histological diagnosis of oral lichen planus.

## Discussion

In this case, a patient on warfarin was prescribed two drugs by his GDP, both of which had the potential to interact with the metabolism of warfarin. The consequence of this was an increase in the level of anticoagulation, with an INR above the recommended therapeutic range. This resulted in the bruising of the patient's torso, following trauma, which alerted him to a potential interaction, as outlined in the drug information leaflets.

Warfarin is the most widely prescribed anticoagulant drug for thrombo-embolic therapy in Europe. It is used to treat deep vein thrombosis and pulmonary embolism.<sup>2</sup> Warfarin can also be prescribed

to patients that have had recent cardiac problems; after certain surgical procedures; patients with irregular heart rhythms (atrial fibrillation)<sup>3</sup> and after heart valve replacement surgery.<sup>4,5,6</sup>

Warfarin is an antagonist of vitamin-K, and exhibits its effect by preventing the synthesis of several active vitamin-K dependant clotting factors (II, VII, IX and X). It is taken orally and has a long half-life of approximately 40 hours. Owing to its variable pharmacokinetics, patients taking warfarin have to be regularly monitored via a well recognized blood test – the International Normalized Ratio (INR). This is used to ensure that a patient is at an appropriate level of anticoagulation for the specific medical condition.<sup>4</sup>

Certain medications are known to have adverse interactions with warfarin due to their effect on P-450. For example, antifungal agents can inhibit metabolism and so prolong the warfarin effects, whereas carbamazepine and phenytoin induce metabolism so that the anticoagulant effect is reduced. An increased INR increases the risk of bleeding. Increasing the INR by 1.0 approximately doubles the risk of bleeding. A patient with INR higher than 6.0 has a substantial, short-term risk of major haemorrhage.<sup>6,7</sup> A decreased INR carries the risk of the blood clotting which could lead to formation of a clot or embolism such as a deep vein thrombosis or a pulmonary embolism.

The oral antibiotic drug metronidazole has a well-documented interactive potential with warfarin by inhibiting its metabolism: specifically the ring oxidation of S (-) isomer.<sup>2</sup> As the presence of warfarin is prolonged, this enhances the anticoagulant effects. A high INR can develop within three days of starting metronidazole.<sup>8</sup> In addition, many prescribed antibiotics cause an alteration to the gut flora, which may then interfere with the absorption of vitamin-K. If there is less vitamin-K present in the liver, warfarin can have more of an effect, leading to a decreased production of clotting factors. The use of metronidazole is therefore best avoided in patients on warfarin therapy.

Similarly, miconazole oral gel (Daktarin®) can increase a patient's INR and bleeding potential. Although it is used topically, systemic absorption can occur when the oral mucosa is inflamed or from

the bowels if the gel has been swallowed.<sup>9</sup> Miconazole is an antifungal agent; its effect on warfarin is mediated by blocking the P-450 cytochrome enzyme system in the liver,<sup>10</sup> which decreases the rate that warfarin is metabolized, thereby increasing its anticoagulant effects. If there is a risk of a significant drug interaction with warfarin, then the polyene antifungal agent nystatin suspension should be prescribed.<sup>5</sup>

The metabolism of warfarin is not solely affected by drugs; several foodstuffs and alcohol can also interact with this drug.<sup>11</sup>

When prescribing any drugs, a dentist should always check whether there is any potential for interactions with the patient's existing medications. A patient's medical history, including any medication taken, should be rechecked at every appointment. If there is any doubt about the potential for drug interactions then the British National Formulary should be consulted, ie Appendix 1: Drug Interactions.<sup>12</sup> Further advice can be sought by calling the local telephone number for the Medicines Information Services or visiting [www.ukmi.nhs.uk/activities/specialistServices/](http://www.ukmi.nhs.uk/activities/specialistServices/)

Patients taking warfarin may have oral or dental conditions requiring antibiotics or antifungals, both of which may affect the metabolism of the drug and therefore cause fluctuations in coagulation. It is therefore important that the risks and benefits of prescribing such drugs are carefully assessed and possible alternatives considered.

Prescribing in general dental practice can be a challenge, and clinicians should be aware of drug interactions which could have potentially serious consequences. In this reported case, the patient was at an increased risk of haemorrhage. Equally, by stopping his warfarin, this patient was at risk of a rebound thrombo-embolic event. If the patient had not read the drug information leaflet, and had continued taking his warfarin then his INR could have potentially been increased to a dangerously high level.

This case report highlights the need for prescribing vigilance and continuous professional development in relation to prescribing, especially in respect to drug interactions. There is currently a debate as to whether the GDC five year



**Figure 1.** Bruising of the patient's right torso.



**Figure 2.** Erosions and desquamative gingivitis affecting the hard palate.

cycle of CPD should include a mandatory section on keeping up-to-date with new medications and current prescribing guidelines.

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