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An Interesting Potential Reaction to Warfarin

Abstract: Warfarin is an oral anticoagulant, used routinely for patients with atrial fibrillation, deep vein thrombosis, pulmonary embolism and those with a mechanical prosthetic valve. There are several noted adverse reactions associated with its use, in particular the risk of haemorrhage. Other adverse reactions include: hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haematocrit, purple toes, skin necrosis, jaundice, hepatic dysfunction, nausea, vomiting and pancreatitis. In this case report, an interesting potential adverse reaction to warfarin is discussed. The reaction described affected the patient's tongue, without affecting any other aspect of the oral cavity or body.

Clinical Relevance: This case report highlights the potential problems that can be encountered by patients on warfarin therapy, specifically, the possibility for hypersensitivity type reactions.

Dent Update 2012; 39: 33–37

Warfarin is an oral anticoagulant used commonly in the general population. Its mode of action is to antagonize the effect of vitamin K and inhibit coagulation. It commonly takes 48–72 hours for the anticoagulant effect to develop fully and is the drug of choice for those patients with deep vein thrombosis, pulmonary embolism, atrial fibrilliation or for patients with a mechanical prosthetic valve.[1]

The main adverse effect associated with warfarin is the risk of haemorrhage, therefore International Normalized Ratio (INR) levels should be checked regularly and the warfarin dose adjusted accordingly.[2] Other side-effects previously noted with warfarin include:

- Hypersensitivity;
- Rash;
- Alopecia;
- Diarrhoea;
- Unexplained drop in haematocrit;
- Purple toes;
- Skin necrosis;
- Jaundice;
- Hepatic dysfunction;
- Nausea;
- Vomiting; and
- Pancreatitis.[1]

Warfarin is well known to interact with a wide array of medications, including antibiotics and antifungals, and its action can also be affected by diet, in particular foods high in vitamin K, such as liver, broccoli and green leafy vegetables. Alcohol and periods of illness, especially bacterial or viral infections, can also affect the body's response to warfarin, thereby interfering with the INR level.[3] Patients should be adequately counselled before commencing warfarin therapy with regards to diet and lifestyle, and practitioners should be vigilant when prescribing other medications for such patients.

In this case a potential reaction to warfarin in an elderly gentleman is described.

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Case report

In September 2008 a referral was made to the Maxillofacial Department in Altnagelvin Hospital regarding an 86-year-old gentleman suffering from suspected oral candidiasis that was unresponsive to antifungal treatment.

The patient was a retired gentleman who no longer smoked, having given up over 40 years ago, and consumed no alcohol. The patient was not a regular dental attender and was edentulous.

He had been started on warfarin five months previously for atrial fibrillation and he also had a history of heart failure. The patient's other medications included: nystatin pastilles, digoxin, bumetanide and chlorphenamine. An allergy to penicillin was recorded.

On presentation it was noted that the patient had complained of the appearance of an ulcerated tongue starting four weeks previously. This had been treated ineffectively with cetalkonium chloride containing choline salicylate (Bonjela®). As a second option his general medical practitioner (GMP) prescribed miconazole gel, however, the interaction of the antifungal treatment and the warfarin caused the patient's INR level to increase dramatically to over 10. The miconazole was therefore discontinued and replaced with nystatin pastilles. However, there was still no resolution of the oral lesions.

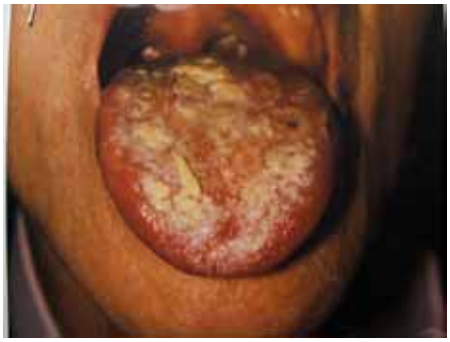

Figure 1. Appearance of patient's tongue at initial presentation to Maxillofacial Department at Altnagelvin Area Hospital.

Examination of the oral cavity revealed the dorsal aspect of the tongue to be ulcerated, with areas of erythroplakia and leukoplakia noted (Figure 1). The ventral surface of the tongue and all other soft tissues were unaffected.

An appointment was made for incisional biopsy of the ulcerated area on the dorsum of the tongue under local anaesthetic with the view to assessing the sample with Haematoxylin and Eosin to determine if there were any morphological changes in the tissue structure and immunoassay. A haematinic screen was sent to assess any underlying deficiency that may have been contributing to the clinical picture, in particular deficiencies of iron, folate and B vitamins.

From the blood results the only variable of note was a raised ferritin level, despite no recent iron therapy. The haematologist was consulted with regards to this highly elevated level, however, it was explained that this could be increased in an acute phase reaction (inflammatory response) and no active treatment was needed.

The day before the patient was to attend for biopsy, the INR level was measured at 7.0. The procedure was therefore postponed and a new date was given for two weeks later.

At the review appointment there was a dramatic improvement in the appearance of the tongue, although there was still some residual ulceration on the dorsal surface.

It was noted that the patient had not been taking his warfarin, at the request of his GMP, in an effort to lower the INR level prior to the biopsy. This incidental finding lead to a revised treatment plan, which involved discontinuing his warfarin and replacing this medication with aspirin and clopidogrel, under the guidance of his haematologist.

At the subsequent appointment, 2 weeks later, the tongue lesions had entirely resolved and biopsy was therefore felt to be no longer indicated. The patient was discharged back to his own GMP for regular follow-up.

Discussion

This case presents unusual tongue lesions, which appear to have manifested as a direct result of warfarin therapy. Adverse reactions associated with warfarin therapy can be broadly classified under two headings, namely, haemorrhagic and non-haemorrhagic. The most common haemorrhagic complication is GI bleeding.[3] Non-haemorrhagic reactions include:

- Allergic maculopapular eruption;
- Urticaria;
- Eosinophilic pleuritis;
- Vasculitis;
- Toxic hepatitis;
- Skin necrosis; and
- Purple toe syndrome.[3]

There are many reports in the literature describing oral effects associated with medications. Adverse drug reactions presenting in the oral cavity include xerostomia, swelling, ulceration, vesiculobullous or ulcerative mucositis that mimics other disease states, vesiculo-ulcerative states, pigmentation, gingival enlargement and osteonecrosis of the jaw.[4–8]

Epithelial necrosis and ulceration is a possible sequela of drug contact with the mucosa and is commonly seen in patients holding aspirin in the buccal sulcus adjacent to the affected tooth for dental pain. The mucosa appears white and thickened with areas of ulceration and erosion. Classically, the posterior buccal mucosa, lateral borders of the tongue and the alveolar mucosa are involved, but any oral site can be affected. Some oral manifestions of drug reactions mimic other disease states clinically, histopathologically and, in some cases, immunopathologically.[4–8]

It is possible that the lesions noted on the tongue were as a direct response to the use of warfarin. The tongue lesions were not noted for four months after the warfarin had been commenced. However, as the patient was not attending a general dental practitioner (GDP) regularly, and as pain was not a presenting symptom, there is no way of knowing exactly when the appearance of the tongue began to change. The lesions on the tongue did not respond to the standard remit of remedies for candidiasis, however, on stopping the warfarin, the effect was relatively rapid, with resolution noticed within a matter of days. The only way to prove that the tongue lesions were directly related to the use of warfarin conclusively would be to re-challenge the patient with warfarin, however, this is not an ethical option.

Skin necrosis, purple toe syndrome and maculopapular skin reactions are known, but infrequent, potential reactions to warfarin therapy. Despite some similarities in their presentation, they are caused by different mechanisms and have different times of onset.[9]

Skin necrosis is a rare, but severe, complication of warfarin treatment. The reaction usually starts within 3–10 days of commencing therapy and initially presents as painful red lesions that progress to develop a sharp border and become petechial then hard and purpuric. Within a day the lesion may become clearly necrotic and have blood-filled blisters.[3,10,11] Warfarin therapy should be stopped. Small lesions may resolve spontaneously, however, large lesions can require surgical debridement. In 80% of cases, the lower half of the body is affected, in particular areas of abundant subcutaneous fat such as the buttocks, thighs and abdomen. Skin necrosis is more common in women, particularly obese women and middle-aged women. One third of patients presenting with these lesions have been found to have a deficiency in protein C.[3,10,11]

Purple toe syndrome usually develops 3–8 weeks after starting therapy and is characterized by a painful purple-blue discoloration of the toes. This usually affects patients with vascular atherosclerosis who are receiving warfarin

therapy. If warfarin is discontinued the pain will resolve but the discoloration will persist.[12]

Maculopapular skin eruption is another known, but rare, adverse reaction associated with warfarin therapy and was first documented in the literature in 1959.[13] Lesions are described as transient maculopapular or urticarial reactions that are often purpuric and can be associated with vesicular lesions. Presentation ranges from 40 minutes to 28 days after warfarin therapy is commenced.[9] Normally this reaction begins at the extremities and progresses to the truncal areas and can involve the oral cavity where it presents as erosive lesions.[14] A case by Adams and Pass described a patient who presented 27 days after commencing anticoagulant therapy with pruritic, maculopapular, erythematous eruption on the face, neck, hands and forearms. On oral examination, superficial erosions were noted on the buccal mucosa. All lesions resolved on stopping the therapy.[14]

The patient we described presented only with lesions on the tongue, other oral soft tissues were not affected. Presentation occurred four months after the instigation of the warfarin therapy, however, a history of pain, urticaria or skin lesions was never given. Similar to the cases of maculopapular skin eruption discussed above, the patient we described had a delayed onset of presentation, the lesions resolved spontaneously when the warfarin was discontinued and oral erosions were noted.

Other interesting points of note include:

- The patient was prescribed miconazole for suspected candidal infection despite already being on warfarin. The potential interaction between these two drugs is clearly outlined in the BNF and clinicians should be more vigilant when prescribing drugs to patients receiving polypharmacy.
- Clopidogrel and aspirin have now been substituted for warfarin under the guidance of his haematologist. It must be considered whether this drug substitution is in the patient's best interests as oral vitamin K agonists are the gold standard form of stroke prevention therapy in patients with atrial fibrillation.

Conclusion

The patient described in this case complained of the appearance of an ulcerated tongue four months after warfarin therapy for his atrial fibrillation was commenced. On stopping the warfarin the symptoms began to resolve and, within four weeks, the tongue returned to normal. No other treatment had any effect on the tongue's appearance and no notable change to the patient's lifestyle or medication, other than discontinuing the warfarin, was made to account for the resolution of the tongue lesions. It could therefore be postulated that the reaction seen in the tongue was directly related to the use of warfarin. We highlight this case for oral practitioners to be wary of the possible side-effects of warfarin treatment on the oral mucosa and tongue.

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