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Warfarin-flucloxacillin interaction presenting as cardioembolic ischemic stroke

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Both warfarin and flucloxacillin are frequently prescribed medications which have the potential to have life threatening interactions. We describe a case of sub-therapeutic anti-coagulation following a course of oral flucloxacillin, resulting in an ischemic stroke. A 68-year-old female on long term anti-coagulation for atrial fibrillation presented with an acute left hemiparesis. International normalised ratio (INR) was 1.4 in the emergency department. She had commenced a 14-day course of oral flucloxacillin 500 mg qid and oral phenoxymethylpenicillin 999 mg qid for a soft tissue infection of her foot 17 days prior to admission. The most recent INR taken 19 days prior to admission was 3.5.

The patient's anti-coagulation regimen had been managed by a hospital based clinic. A target INR of 2–3 had been maintained with doses of 4 and 3 mg on alternate days for a period of over 6 months with monthly INR checks. Past medical history included diabetes mellitus type 2, tissue mitral valve replacement, myocardial infarction and hypercholesterolaemia. Her concomitant medications were quinapril, atorvastatin, metoprolol, lercardipine, spironolactone, bumetanide, digoxin, metformin, gliclazide and

biphasic isophane insulin. The patient did not report any other recent change in medication, any change in diet or alcohol intake and no change in warfarin brand. She had not experienced any gastrointestinal illness and reported good compliance with her medication regimen.

No alternative stroke mechanism was identified following extensive investigation including carotid duplex, magnetic resonance brain imaging (MRI), magnetic resonance angiography (MRA), and trans-thoracic echocardiography.

Using the Drug Interaction Probability Scale, a rating of 7 in this case indicates a probable causative interaction [1]. On review of the patient's pharmacy, medical and anti-coagulation clinic records, it was noted that oral flucloxacillin and phenoxymethylpenicillin had previously been prescribed for the patient 6 weeks prior to admission. On that occasion an INR of 1.8 was recorded 5 days after completing the course of antibiotics.

A case of suspected interaction between oral flucloxacillin and warfarin has been recently reported [2]. Review of the literature reveals one further description of sub-therapeutic anti-coagulation when flucloxacillin and a coumarin were prescribed concurrently. The authors in that case attributed the fall in INR to concomitant rifampicin, however the role of flucloxacillin may have been underestimated [3]. Flucloxacillin has the potential to induce expression of cytochrome P450 3A4 which is the enzyme which catalyzes the 10-hydroxylation of *R*-warfarin [4, 5].

The inflammatory response to infection and individual genetic variation may influence warfarin metabolism by pharmacokinetic or pharmacodynamic mechanisms [1, 6]. In this case the infection treated was a localised skin infection with no evidence of a systemic inflammatory response or underlying osteomyelitis. Sub-therapeutic anti-coagulation has been reported previously with warfarin and

This work has not been published or presented previously.

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nafcillin and dicloxacillin, other narrow spectrum beta-lactam antibiotics [7, 8].

This case further demonstrates the potential for interaction between warfarin and flucloxacillin resulting in sub-therapeutic anti-coagulation. Amoxicillin has been reported to enhance the effects of warfarin rather than to diminish its effects, and the role of phenoxymethylpenicillin in the case is not clear [9, 10]. We suggest vigilance when any medication is begun or discontinued in a patient on warfarin therapy by health care professionals involved in prescribing and monitoring of anti-coagulation.

Conflict of interest No conflict of interest is reported.

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