Significant interaction between amoxicillin/clavulanate and warfarin: A case report highlighting international normalized ratio elevation and management strategies

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SUMMARY

This case report emphasizes a notable interaction between amoxicillin/clavulanate and warfarin, leading to a substantial elevation in INR values from a baseline of 1.4 to 7.9. The increase in INR highlights the influence of amoxicillin/clavulanate on the anticoagulant effects of warfarin, which is likely the result of its disruption of gut flora and vitamin K metabolism. After the transition to flucloxacillin, an INR reduction to 3.0 was noted, this fall in INR levels was consistent with the latest studies suggesting the reduced impact of flucloxacillin on INR. The stabilization of the patient's INR following the change in antibiotics suggests that flucloxacillin is comparatively safer for individuals on warfarin.

INTRODUCTION

Warfarin is an oral anticoagulant widely used for the prevention and treatment of thrombosis. Globally, warfarin is one of the most frequently used oral anticoagulants for long-term therapy[1] In 2022, an analysis across 12 European Union countries was done and it showed that Warfarin is still the primary oral anticoagulant in 20–40% of patients requiring long-term anticoagulation, particularly in patients with mechanical heart valve.[2] In the United Kingdom, approximately 1% of the general population and 8% of those over 80 years are prescribed warfarin.[3]

In Europe, guidelines from the European Society of Cardiology recommend its use in specific indications such as mechanical heart valves, while Direct Oral Anticoagulants (DOACs) are replacing warfarin in other settings.[4,5] Monitoring the International Normalised Ratio (INR) is crucial during warfarin therapy. The dosage is adjusted to maintain INR within the therapeutic range to avoid thrombotic or haemorrhagic complications.[4]

Antibiotics may interact with warfarin, leading to significant INR changes. Multiple reports document elevation of INR levels and/or haemorrhage associated with combined amoxicillin and warfarin use.[5,6] Amoxicillin is recognised for its effect on INR, whereas amoxicillin/clavulanate which is a combination beta-lactam/beta-lactamase inhibitor, has less comprehensive literature regarding its isolated impact on INR levels.

This case report seeks to investigate the effect of amoxicillin/clavulanate on INR in a patient undergoing warfarin therapy for thromboembolic event prophylaxis. This example highlights the importance of closely monitoring INR levels and adjusting warfarin dosages as needed when administering amoxicillin/clavulanate to ensure both patient safety and effective anticoagulation.

CASE PRESENTATION

A 93-year-old man presented to the emergency department after having a mechanical fall at home. He reported losing his balance while attempting to get into bed; there was no prodromal dizziness and he was alert and orientated on arrival. His medical history comprised pulmonary embolism (on long-term warfarin alternate day dosing of 1 & 2mg), Ischaemic heart disease, type 2 diabetes, osteoarthritis, age-related macular degeneration and cataracts.

During admission, he developed a productive cough and low-grade pyrexia. He was found to be SARS-CoV-2 positive on PCR. Inflammatory markers on admission showed leucocytosis and an elevated c-reactive protein (Neutrophils 8.2x 10^9/L, CRP - 280mg/L). Empirical oral amoxicillin/clavulanate with a dosage of 625 mg three times a day was initiated in accordance with local guidance for suspected bacterial pneumonia complicating COVID-19. Baseline International Normalised Ratio (INR) four days earlier was 1.4. After Day 1 of amoxicillin/clavulanate the INR rose to 5.7, peaking at 7.9 on Day 2 and reaching 7.5 on Day 3. Warfarin was withheld; no overt bleeding occurred and phytomenadione 1mg was administered to counter the elevated INR.

Potential contributors to the supra-therapeutic INR such as reduced dietary vitamin K intake was confirmed by reviewing each patent's dietary intake such as diet history and diet documentation but no significant changes in diet patterns were recorded due to the patient being on a diabetic hospital diet. To rule out hepatic dysfunction as a contributing factor, liver and renal functions were observed to be within the reference limits as indicated by stable liver enzymes levels (AST, ALT, Bilirubin). Finally, medication non-adherence was considered through self-reporting of patient's pill counts but none appeared contributory.

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Table I: Trend of INR Levels in response to amoxicillin/clavulanate and flucloxacillin treatment

Day	Drug Administered	INR Value	Interpretation
Baseline (4 days before)	None	2.0	Pre-treatment baseline INR value.
Day 1 of Amoxicillin/Clavulanate	amoxicillin/clavulanate	5.5	Elevated INR following start of amoxicillin/clavulanate.
Day 2 of Amoxicillin/Clavulanate	amoxicillin/clavulanate	7.9	Peak INR observed; concern for increased bleeding risk.
Day 3 of Amoxicillin/Clavulanate	amoxicillin/clavulanate	7.5	Slight decrease, received 1mg phytomenadione.
Day 1 after switch	flucloxacillin	6.6	Switched to flucloxacillin; INR begins to decline.
Day 3 after switch	flucloxacillin	3.0	INR significantly decreased, trending toward normalization.

Further, computed tomography of the thorax and abdomen revealed no intra-abdominal or intrathoracic source of sepsis. Persistent fever prompted re-examination, which demonstrated erythematous swelling of the right forearm consistent with cellulitis. Amoxicillin/clavulanate was discontinued and oral flucloxacillin 1000 mg every 6 hours was commenced.

Following the antibiotic switch the INR declined to 6.6 on Day 1 and to 3.0 on Day 3, with subsequent readings remaining within the therapeutic range. No INR-related complications were observed and warfarin therapy was resumed at the patient's usual dose once the INR stabilised.

DISCUSSION

The observed increase in INR from 1.4 to 7.9 within two days of initiating amoxicillin/clavulanate highlights a significant interaction between this antibiotic and warfarin. The increase in INR observed in our patient can be attributed to amoxicillin/clavulanate's effect on gut flora and vitamin K metabolism.[7] Although gut flora plays an important part in the conversion of vitamin K, liver enzymes have also been said to play an equally significant role in the metabolism of vitamin K. Patients with liver failures as a result of lack of liver enzyme excretion disrupts the metabolism of vitamin K in their bodies.[6]

Most penicillin-class antibiotics can boost warfarin's effects, thereby increasing the risk of bleeding, especially when administered intravenously.[10] This results in decreased vitamin K producing bacteria, which in turn leads to reduced amount of vitamin K absorbed, and thus manifests as vitamin K deficiency; the exception to this is dicloxacillin and nafcillin, which reduce the efficacy of warfarin by increasing warfarin's metabolism.[6,7]

After the switch from amoxicillin/clavulanate to flucloxacillin, a significant reduction in INR from 6.6 to 3.0 was observed over a period of three days.

1. Timeline of Antibiotic Initiation vs INR Rise
Written pharmacologic expectations suggest that transient antibiotic administration (such as amoxicillin/clavulanate) usually takes several doses to significantly inhibit gut flora and affect vitamin K levels. In your case, INR rose dramatically within 24 hours, after just the first few doses (INR 5.5 after <24 hours and 5 doses by Day 2; peaked at 7.9 by Day 2). This is earlier than typical but aligns with acute potentiation of warfarin metabolism or altered pharmacodynamics.

2. Resolution after Antibiotic Switch
The INR decline after switching from amoxicillin/clavulanate to flucloxacillin, without new antibiotic exposures, supports a direct drug–warfarin interaction rather than delayed drug-induced INR rise or COVID-only effects.

This data corroborates existing literature suggesting that Flucloxacillin exerts minimal impact on INR in contrast to amoxicillin/clavulanate. Mannheimer et al. (8) found that flucloxacillin exerted minimal effects on INR in warfarin users, consistent with our findings.8 In contrast, a case report from China states that β-lactam or β-lactamase inhibitors like amoxicillin/clavulanate and piperacillin or tazobactam generally produce a more substantial increase in INR. The clavulanate component in amoxicillin/clavulanate inhibits bacterial β-lactamases, further disrupting gut flora and leading to reduced vitamin K synthesis. Similarly, piperacillin or tazobactam have been associated with coagulopathy through a vitamin K-dependent mechanism. Thus, while flucloxacillin can alter INR levels due to microbiome disruption, its effect is typically less significant than that observed with other β-lactamase inhibitors.[9]

While COVID–19–associated coagulopathy may have contributed to baseline warfarin destabilization, the very sharp rise and rapid fall in INR aligning with antibiotic change favour a primary pharmacologic interaction, rather than a slower, more diffuse COVID-driven INR elevation. COVID-19 is known to induce a pro-inflammatory and pro-thrombotic state, frequently disrupting coagulation pathways, including elevated D-dimer, CRP, and derangements in INR control, even in the absence of interacting medications.[10] Several reports have shown that patients on warfarin may experience supratherapeutic INR levels during acute COVID-19 infection due to increased sensitivity or decreased clearance of the drug.[10] While this may have contributed to the observed INR rise, the sharp elevation shortly after starting amoxicillin/clavulanate and its subsequent decline following antibiotic withdrawal support a pharmacologic interaction as the primary driver.

This example highlights the necessity of careful INR monitoring when antibiotics are administered to individuals on warfarin. Amoxicillin/clavulanate and warfarin must be carefully managed to prevent any problems that could arise from high INR levels. Clinicians should anticipate potential INR fluctuations when commencing or modifying antibiotic treatment and adjust warfarin dosages accordingly to maintain therapeutic INR levels.

CONCLUSION

The normalization of the patient's INR following the alteration of antibiotics indicates that flucloxacillin is comparatively safer for individuals on warfarin. It is advised that clinicians modify INR monitoring protocols while initiating or adjusting antibiotic treatment in patients on warfarin. This is especially crucial with antibiotics that notably affect INR levels, such as amoxicillin/clavulanate. Consistent monitoring and prompt modification of warfarin dosage can avert problems associated with elevated INR and provide safe therapeutic treatment.

Further research is required to examine the comprehensive interactions between antibiotics and warfarin, especially those involving prolonged or intricate treatment protocols. Examining the mechanisms regulating these interactions and their clinical ramifications may yield better guidelines for managing INR and enhancing patient safety. Subsequent research should concentrate on evaluating the effects of different antibiotics on INR levels across diverse patient demographics to improve our comprehension and management of anticoagulant treatment.

CONFLICT OF INTEREST

None

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DECLARATION

We affirm that this work is original, and consent was obtained from the patient. There were not any conflict of interest by the authors.

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