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Fluindione and cefixime induced cutaneous bleeding manifestations –A case report and review of literature

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Abstract

Fluindione an oral vitamin K antagonist is associated with various hemorrhagic and immunoallergic effects. This drug is also prone to produce various drug interactions, which if not taken into consideration while prescribing, might lead to increased incidence of adverse drug reactions for the patients. We report a case of drug interaction between fluindione and cefixime leading to cutaneous bleeding manifestations and raised PT-INR. Our patient was a 59 year old lady, a known case of rheumatic heart disease and mitral valve replacement, on tablet fluindione 20 mg for past 11 years. She was prescribed tablet cefixime 200 mg two times a day for three days for treatment of upper respiratory tract infection, following which she developed cutaneous bleeding manifestations like ecchymosis and purpura in left upper and lower limbs. She also had a rise in PT-INR level to 4.2, predisposing the patient to life threatening bleeding manifestations. Hence, caution is warranted while prescribing antibiotics to patients on oral anticoagulant therapy. Antibiotics that do not cause drug interaction with the anticoagulants must be selected in these patients. Also, periodic monitoring of PT INR in patients on anticoagulants especially when a new drug is co-prescribed is essential to curb the hazards of potential adverse drug interaction.

Keywords: Fluindione, Vitamin K antagonist, Cefixime, Antibiotics, Drug interactions.

1. Introduction

Fluindione, an indandione derivative oral vitamin K antagonist prescribed for the treatment of cardiovascular diseases and venous thromboembolism is associated with various hemorrhagic and immunoallergic adverse effects. [1] Fluindione exhibits drug interactions with various group of drugs especially antibiotics like erythromycin, metronidazole, clindamycin and tetracycline. It has not yet been proven to interact with broad-spectrum antibiotics like penicillin, aminoglycosides, and cephalosporins. [2] However, we report a case of drug interaction between fluindione and cefixime leading to cutaneous bleeding manifestations.

2. Case Report

A 59 yrs old post menopausal lady presented with complaints of cutaneous bleeding manifestations like purpura and ecchymosis in upper and lower limbs for the past 2 days. Past history revealed that she is a known case of rheumatic heart disease and mitral valve replacement, on tablet fluindione 20mg for past 11 yrs and PT-INR maintained at 2-3. She also informed that she had developed upper respiratory tract infection for which she was prescribed tablet cefixime 200mg twice daily for 3 days. Immediately after intake of 2 doses of cefixime, she developed the cutaneous bleeding manifestation in the left upper and lower limbs.

She had no clinical manifestations of internal bleeding like bleeding gums, malena or hemoptysis. She was taking salmeterol/fluticasone 500 mcg (inhaler) for past 11 yrs for her bronchial asthma. Also, she is on tablet levothyroxine 25microgram for hypothyroidism for past 2 years.

On examination, an ecchymotic patch measuring 8×3cm was present over the medial aspect of left leg. (Figure 1) Another ecchymotic lesion measuring 1x2 cm and a purpuric lesion measuring 1x1cm were present over ventral aspect of left forearm. (Figure 2) Another purpuric lesion measuring 2x2 cm was present over the medial aspect of left thigh. (Figure 3) Her vitals were stable with pulse rate of 80/min, blood pressure of 130/90mmHg and respiratory rate of 20 breaths/min.

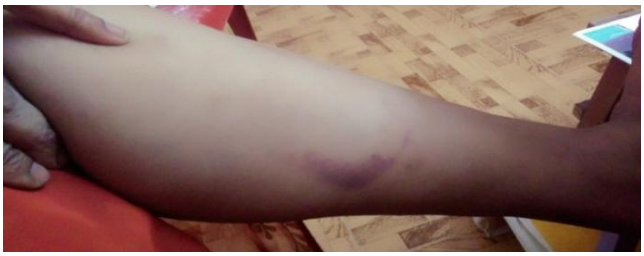

Figure 1: An ecchymotic patch measuring 8×3cm was present over the medial aspect of left leg

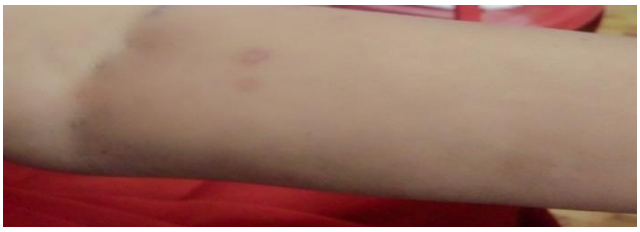

Figure 2: One ecchymotic lesion measuring 1x2 cm and another purpuric lesion measuring 1x1cm were present over ventral aspect of left forearm

Figure 3: Purpuric lesion measuring 2x2 cm was present over the medial aspect of left thigh

On investigation, PT-INR was raised when compared to previous month report. PT-INR was 2.5 before taking cefixime, whereas it rose to 4.2 after cefixime administration. Cefixime was discontinued and fluindione was stopped temporarily for 2 days. Bleeding manifestations slowly started resolving and fluindione was restarted at the same dose. Follow up PT-INR after one week reduced to 3. Patient recovered completely without any sequelae.

3. Discussion

Fluindione, an oral vitamin K antagonist is used for the treatment of cardiovascular diseases like rheumatic heart disease and venous thromboembolism. [1] The target PT-INR for rheumatic heart disease patients who are on oral anticoagulant therapy should be maintained in the range of 2.5-3.5. PT-INR needs to be checked daily, until therapeutic range has been achieved and sustained for 2 consecutive days. Subsequently, it is checked 2-3 times weekly for 1-2weeks, and then less often. Once PT-INR is stable, the frequency of testing can be reduced to once in 4 weeks. However, a wide range of drugs can interact with oral vitamin K antagonists and alter the PT-INR values for the patient, which can lead to severe life threatening bleeding manifestations for the patient. [3]

Cefixime is a third generation cephalosporin antibiotic indicated in treatment of upper respiratory tract infections. It has the potential to cause bleeding manifestations and raise the PT-INR when co-prescribed to patients on fluindione therapy. [4] It is also reported that cefixime increases the anticoagulant activity of the drug phenendione which also belongs to the class of indandione derivative of anticoagulant drugs. [5] The exact mechanism of such interaction remains unknown and literature on drug interaction between fluindione and cefixime is limited. The drug interaction does not seem to be due to the influence of the drugs on microsomal enzymes. Fluindione is metabolized predominantly by CYP2C9 isoenzyme. [6] According to a study by Niwa *et al*, it is found that cefixime does not affect the pharmacokinetics and metabolism of drugs metabolized by CYP2C 9. [7] Thus it is evident that the interaction is not due to inhibition of drug metabolism.

Nevertheless, various mechanisms for the drug interaction have been postulated. Studies have shown that antibiotic medications like cefixime interact with oral anticoagulants to increase the risk of major bleeding through disruption of intestinal flora that synthesize vitamin K. [8] Various intestinal bacteria like Bacteroides fragilis and Escherichia coli have been shown to synthesize vitamin K which partially counteracts the effect of the anticoagulant. However, on concomitant administration of cefixime, these intestinal bacteria are destroyed and the antagonizing effect of vitamin K on the anticoagulant drugs is lost. Thus, it leads to increased anticoagulant effect and manifests as bleeding episodes. [9-12]

Another mechanism which has been postulated for the drug interaction is that cefixime as such has the potential to cause bleeding manifestations by reducing the platelet count.[4] Thus, the thrombocytopenic action of cefixime along with the exaggerated anticoagulant effect of fluindione in the presence of cefixime can be attributed to

the bleeding manifestations and raised PT-INR in this patient.

The probability of adverse drug reaction (cutaneous bleeding manifestation) occurring due to a drug interaction between fluindione and cefixime was assessed by the Drug Interaction Probability Scale (DIPS). [13]

Drug Interaction Probability Scale (DIPS) scoring:

1) There were previous credible reports of this interaction. (+1)
2) The observed interaction was consistent with the known interactive properties of precipitant drug.(+1)
3) The observed interaction was consistent with the known interactive properties of object drug.(+1)
4) The event was consistent with the known or reasonable time course of the interaction.(+1)
5) The interaction remitted upon dechallenge of the precipitant drug with no change in the object drug.(+1)
6) The precipitant drug was not re-administered in the presence of continued use of object drug.(0)
7) No other reasonable alternative causes for the event.(+1)
8) The object drug was not estimated in the blood or other fluids.(0)
9) The drug interaction was confirmed by an objective evidence (raised PT-INR) consistent with the effects on the object drug (+1)
10) The precipitant drug dose was not adjusted.(0)

Thus the total Drug Interaction Probability Scale (DIPS) score is 7.

According to the Drug Interaction Probability Scale (DIPS), the likelihood of the adverse drug reaction occurring due to the drug interaction is as follows:

>8: Highly Probable
5-8: Probable
2-4: Possible
<2: Doubtful

Based on the total score of 7 according to the Drug Interaction Probability Scale (DIPS), the likelihood of the adverse drug reaction occurring due to drug interaction between fluindione and cefixime was categorized as **"probable".**

This adverse drug reaction could have been prevented by careful selection of antibiotics which does not interact with oral anticoagulants. The antibiotics which could be prescribed in patients on oral anticoagulants are penicillins and aminoglycosides. [2] Moreover, when antibiotics are administered to patients on oral anticoagulants, strict monitoring of PT-INR values becomes essential to prevent adverse drug reactions.

4. Conclusion

Bleeding manifestations with oral anticoagulants are common especially on co-administration with other drugs. However, adverse drug reactions due to the drug interactions are definitely preventable by judiciously choosing the concomitant drugs, such that they do not produce drug interaction. Thus, knowledge of drugs interacting with oral anticoagulants is very much essential and should be taken into consideration before prescribing them to the patients on long term maintenance therapy of anticoagulants. In case, of co-administration of other drugs with oral anticoagulants, it is mandatory to monitor PT-INR for the patient to prevent adverse effects.

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