

RESEARCH ARTICLE

**Lactulose induced warfarin toxicity- an interesting drug interaction**

**Kiran Shivaraj, Muhammed Faizan Ahmed**

*Department of internal Medicine, Brookdale Hospital Medical Center, Brooklyn, NY, USA.*

**ABSTRACT**

Warfarin one of the most commonly used anticoagulants in the world is affected by the vitamin K levels in the body, which in turn depends upon many factors like drugs and diet. Here we present a case of a drug interaction between 2 commonly drugs especially in the elderly population. In this case Lactulose interacts with absorption of vitamin K from the gut and thereby potentiating the effect of warfarin toxicity. Hence it is important for every physician to be aware of this drug interaction and warn their patients regarding the same.

**KEY WORDS:**

Lactulose, vitamin K, toxicity, anticoagulants, drug interaction, laxatives

**History**

Received: 30 September 2019

Accepted: 12 January 2019

Published: 17 January 2019

**Volume : 6 Issue : 1**

**BACKGROUND**

Warfarin which acts by inhibiting the enzyme vit K epoxide reductase and thereby decreasing the production of factors II, VII, IX and X<sup>1</sup> has been used as an anticoagulant ever since its approval for human use in 1954. With the introduction of Novel oral anticoagulants, the usage of warfarin has reduced significantly, except for certain indication where warfarin is still the drug of choice<sup>2-3</sup>. The dosage and the effect of warfarin depends upon the factors which affect the level of vitamin K in the body. We commonly find the interaction of warfarin with food containing high vitamin K leading to subtherapeutic levels of anticoagulation<sup>4</sup>. The absorption of vitamin K depends upon factors like fat absorption and intestinal transit time. As per a study done by Loes E Visser et. al<sup>5</sup> lactulose decreases the absorption of vitamin K from the gut partly by increasing the gut transit time. We present an interesting case of a patient who presented with warfarin toxicity secondary to lactulose cotherapy.

**CASE PRESENTATION**

A 78 year old female patient presented to us from the Nursing home with altered mental status and history of constipation for 5 days. She had a past medical history of Atrial fibrillation started and was started on warfarin for stroke prevention<sup>6</sup> with last INR checked 5 days back, which was 2.7 (therapeutic range of 2-3). In the nursing home due to the fecal impaction seen on the abdominal x ray (fig 1.) she was started on Lactulose oral solution. Gradually patient developed an altered mental status and hence was referred to the hospital for further

evaluation. On arrival the patient was found to be disoriented with no signs of any focal neurological deficits. When labs were done it showed and elevated INR of >10. In view of altered mental status and elevated and emergent CT head was done, which was negative for intracranial bleed. CT chest abdomen and Pelvis was done, but no source of bleeding was found, but showed a large bowel dilatation due to fecal impaction in the sigmoid colon.. She was given Vitamin K followed by 2 units of Fresh frozen plasma. Upon repeating the labs, the INR had reduced to 2.97 and continued to be below 3. Fecal disimpaction was done after which her mentation and the colonic dilatation improved significantly (Fig. 2) . The warfarin was restarted once the INR was below 2.

**DISCUSSION**

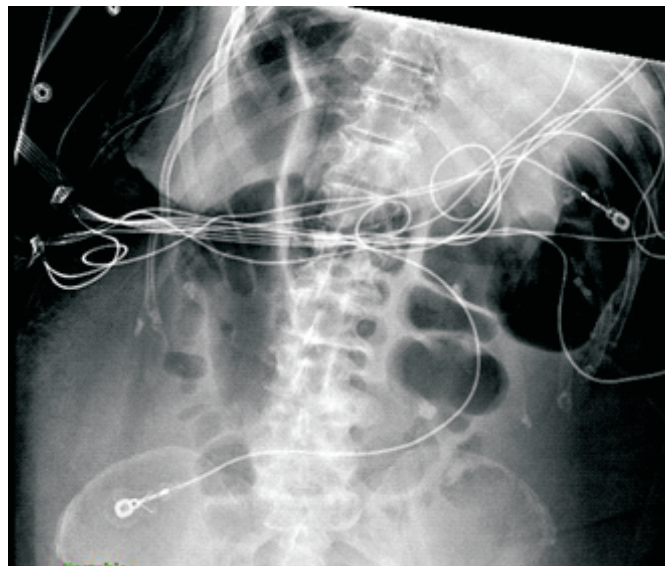
This is a rare case of drug interaction of 2 commonly used drugs, Warfarin and lactulose. warfarin is notorious for drug interaction due to factors like enzyme induction or inhibition, displacement from the protein binding and also due factor affecting vitamin K levels. The drug Lactulose is a disaccharide of fructose and galactose, with commercial lactulose being produced by isomerisation of lactose found in milk. The Lactulose cannot be broken down by the human intestinal enzymes and hence remains in the gut as an osmotic agent which retain in the intestine and thereby acts as an osmotic laxative. A study done by Meril M et al<sup>7</sup> found that when lactulose were used in patients with cirrhosis, it resulted in significant steatorrhea of >10g/day. Whether lactulose causes the same effect in non cirrhotic individuals is not known. The possible explanation for this phenomenon is the

Address for correspondence: Kiran Shivaraj, Department of Internal Medicine, Brookdale Hospital Medical Center, Brooklyn, NY, USA

rapid transit of the intestinal content through the gut and thereby causing a decreased absorption of fat. Vitamin K which is a known lipid soluble vitamin, will be malabsorbed due to the decrease fat absorption. This inturn leads to enhanced action of Warfarin, leading to its toxicity. Hence through this case we would like to emphasize the fact that the doctors must be aware of the drug interaction between these two commonly used drugs and must use this knowledge to educate their patients regarding the same. Whether this drug interaction is specific for lactulose or can this happen with other laxatives is to be studied.



**Figure 1.** Distension of the bowel due to fecal impaction.



**Figure 2.** Significant improvement of bowel distension after fecal disimpaction.

**REFERENCES**

- [1]. Robert G. Bell Mechanism of action of warfarin. Warfarin and metabolism of vitamin K1 Biochemistry 1972;11(10):1959-1961
- [2]. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH, American College of Chest Physicians. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012;141(2 Suppl):e576S-600S.
- [3]. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guidelines for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American heart association task force on practice guidelines. Circulation 2014;129:2440-92.
- [4]. Greenblatt, D. J., & von Moltke, L. L. (2005). Interaction of warfarin with drugs, natural substances, and foods. The Journal of Clinical Pharmacology, 45, 127–132.
- [5]. Visser LE, Penning-van Beest FJ, Wilson JH, et al. Overanticoagulation associated with combined use of lactulose and acenocoumarol or phenprocoumon. Br J Clin Pharmacol. 2004;57(4):522–524. doi:10.1046/j.1365-2125.2003.02036.x
- [6]. NASPEAF investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and non-valvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol 2004; 44: 1557–66.
- [7]. Merli M et al. The effect of lactulose and lactitol administration on fecal fat excretion in patients with liver cirrhosis. J Clin Gastroenterol. 1992 Sep;15(2):125-7.