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Warfarin Toxicity: Unanticipated Cause of Mesenteric Haematoma, Massive Haemoperitoneum and Small Bowel Haemorrhagic Infarction.

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Abstract: *Oral anticoagulant is often prescribed in patients at risk of thromboembolic diseases, for prophylactic reason. The drug is associated with attendant risk of bleeding as side effect, often due to over dosage or synergistic interaction with other drugs. We report a case of patient on oral anticoagulant, with unsuspected massive mesenteric haematoma, haemoperitoneum and haemorrhagic infarction of small bowel, accidentally discovered at laparotomy.*

Keywords: *Haemoperitoneum, haemorrhagic infarction of small bowel, mesenteric haematoma and Oral anticoagulant.*

I. Introduction

Warfarin an accidentally discovered [1**]** and most commonly prescribed oral anticoagulant in patient with high risk for thromboembolic diseases in western world. **[**2] These include patients with atrial fibrillation, dilated cardiomyopathy, prosthetic cardiac valves among others. The drug has a narrow therapeutic margin and wide range of effective dosage ranging from 1mg to 20 mg daily. [3, 4] The effective dosage of the drug is often influenced by many factors such as genetic susceptibility of an individual, interaction with other drugs, among others. [5] The narrow therapeutic index of warfarin makes it important for regular monitoring of the drug through international normalised ratio (INR) in other to maintain effective therapeutic dosage for each individual and to avoid the risk of haemorrhagic complication. [4] Despite this, the complication of bleeding is still not uncommon in patients taking warfarin. [6, 7] Such bleeding is often inconsequential and rarely fatal. We report a case of 78- year- old man on warfarin who presented with massive haemoperitoneum from ruptured mesenteric haematoma and haemorrhagic infarction of small bowel requiring resection and anastomosis of small bowel at laparotomy

II. Case Report

Our patient was a 78 year old man, being managed for dilated cardiomyopathy by the medical unit. The patient presented to our emergency unit with 2 days history of sudden onset of abdominal pain with no known relieving nor aggravating factor, pain was so severe as to affect activities of daily living. Past bowel movement of the patient was a day prior to presentation and of normal consistency and colour. No other remarkable findings from review of systems, no preceding history of trauma and no history of bleeding from orifices. Review of patients' drug history revealed that patient was on warfarin 10 mg daily on account of previous diagnosis of dilated cardiomyopathy, and was recently placed on non steroidal anti-inflammatory drug (Ibuprofen 400 mg twice daily) from a local chemist shop following complain of bilateral knee joint pain for which he has been taken in last 3 days prior to presentation. On examination patient was found sweating and in painful distress, pale, with pulse rate of 116/minute, blood pressure of 98/60 mm Hg, respiratory rate of 32/minute and temperature of 37.6^{o} C. The abdominal examination shows grossly distended abdomen with physical signs in keeping with generalised peritonitis and absent bowel sound. Rectal examination findings were not remarkable except for boggy recto-vesical pouch. The laboratory investigations ordered for were in keeping with normal white blood cell and platelet count with packed cell volume of 33% and result of electrolytes were not remarkable except for mild elevated urea of 10.6mmol/l. The plain abdominal X-ray findings were in keeping with dilated, thickened small bowel loop with air fluid level and ground glass opacity. The clotting profile showed elevated prothrombin time (PT) with international normalized ratio (INR) of 7.8 which is beyond the normal range, while bed side clotting and bleeding time were 17 minutes and 9 minutes respectively.

Based on our findings, an assessment of generalised peritonitis secondary to perforated peptic ulcer disease in patient with background dilated cardiomyopathy and deranged clotting profile was made. Patient was resuscitated with intravenous crystalloid , intranasal oxygen support and was commenced on

intravenous injection of vitamin K1, while 2 units of fresh frozen plasma and 2 units of fresh whole blood were cross matched for the surgery.

Patient then had emergency laparotomy through upper mid line incision and the intra operative findings were in keeping with massive haemoperitoneum with about 2.1litre of frank blood in peritoneal cavity and mesenteric haematoma with haemorrhagic infarction of about 3 feet of mid jejunum (fig1).

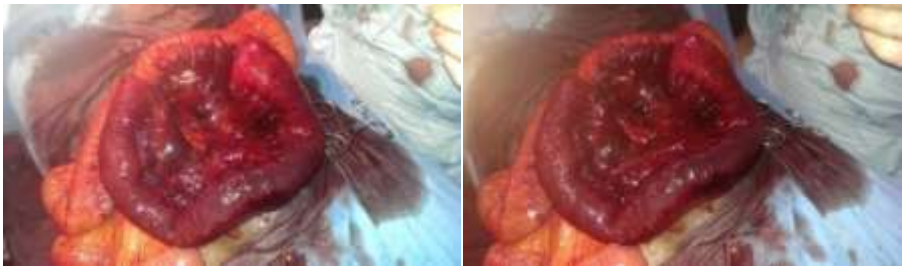

Figure 1 Showing mesenteric haematoma creeping on the small bowel wall

Patient then had resection and anastomosis with 2 units of fresh whole blood transfused intraoperatively and had 2 units of fresh frozen plasma transfused post operatively. Third day post operation patient had 2 episodes of bleeding per rectum and eventually died third day post operation due to haemorrhagic shock from uncontrolled gastrointestinal tract (GIT) bleeding. The post-mortem could not be done for some logistic reasons during this period.

III. Discussions

Warfarin is a commonly prescribed oral anticoagulant with a narrow therapeutic margin. [2,3] Warfarin exert its anticoagulant effect by inhibiting the vitamin k dependent clotting factors by preventing gamma-carboxylation of factors II,VII, IX and X [8] thus prevent the formation of active forms of these factors. Due to the narrow therapeutic margin it's recommended to routinely monitoring the INR of patients on warfarin in the range of 2-3. [9] Bleeding is a common manifestation of warfarin toxicity and often take the form of spontaneous bleeding or unanticipated excessive haemorrhage following minimal invasive procedures such as tooth extraction, intramuscular injection and bleeding into the joint following minimal trauma to the joint and usually inconsequential. Bleeding into the gastrointestinal tract and intracranial cavity is not uncommon especially in patients with previous history of bleeding peptic ulcer diseases and subarachnoid haemorrhage and in such patients warfarin is often considered contraindicated. Gastrointestinal bleeding when occurs is often intramural. Spontaneous gastrointestinal bleeding with mesenteric haematoma and massive haemoperitoneum seen in our case presentation is a rare occurrence.

Though several factors have been implicated for warfarin over anticoagulation such as dose of the drug, interaction with other concomitant drugs especially drugs that inhibit platelet function and older age. The risk of bleeding has been associated with intensity of anticoagulation and become more significant with INR value of greater than 4.0. [10] All this factors were present in our patient and coupled with lack of routine monitoring played a major role in our index case.

The management of warfarin over anticoagulation depends on patients' INR, co-morbidity and presence or risk of significant bleeding. Though most patients will respond to conservative management with dose adjustment with or without vitamin k1 and blood product as set by American College of Chest Physicians guidelines (table 1). [11]

Table 1 American College of Chest Physicians guidelines for treatment of patients with supra-therapeutic anticoagulation

INR	Bleeding present	Recommended action
> therapeutic to 0.5	No	Lower warfarin dose, or omit a dose and resume warfarin at a lower dose when is in therapeutic range, or no dose reduction needed if INR is Minimally prolonged
>5.0 to 9.0	No	Omit the next 1 to 2 doses of warfarin, monitor INR more frequently, and resume a treatment at lower dose when INR is in therapeutic range, or omit a dose and administer 1 to 2.5 mg oral vitamin K1 for patients at increased risk of bleeding (e.g. history of bleeding, stroke, renal insufficiency, anaemia, and hypertension)
>9.0	No	Hold warfarin and administer 2.5 mg oral vitamin K1. Monitor INR more frequently and administer more vitamin K1 as needed, resume warfarin at a lower dose when INR is in therapeutic range
Any	Serious or life threatening	Hold warfarin and administer 10 mg vitamin K1 by slow IV infusion; supplement with Prothrombin complex concentrate, fresh frozen plasma or recombinant human factor VIIa, depending on clinical urgency. Monitor and repeat as needed

When gastrointestinal bleeding complicates warfarin toxicity the bleeding is often intramural and responds to conservative management with bowel rest and dose adjustment [12] and with ACC guidelines. However, in situation where the diagnosis is not considered as a cause of acute abdomen due to low index of suspicion patients may be wrongly subjected to laparotomy with inadequate pre operative preparation for bleeding diathesis, when the patient presents with hemodynamic instability due to massive haemoperitoneum with clinical evidence of bowel gangrene patients will require laparotomy as exemplified in our case.

IV. Conclusion

Bleeding from warfarin toxicity is not an uncommon complication; this can be prevented through close monitoring of INR and proper education of the patients about the toxicity and possible risk of interaction with other drugs and avoidance of indiscriminate use of over the counter drugs especially in elderly patients who are at risk of polypharmacy.

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