

IMPAIRED HAEMOSTASIS - A POTENTIAL RISK WITH CEPHALOSPORINS

Pages with reference to book, From 25 To 26

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The introduction of cephalosporins in therapeutics brought a revolution in the field of medicine, but unwanted and undesirable effects have also been encountered. Of these, a bleeding tendency has been noted with the use of cefamandole, moxalactam and cefoperazone. The mechanism leading to a haemorrhage diathesis has been studied and is attributed to hypoprothrombinaemia secondary to deranged synthesis of vitamin K; and an impaired platelet function caused by damage to the platelet surface leading to altered protein binding. Vitamin K has an external source from diet which provides vit K1 from green vegetables, vegetable oils and wheat bran. Internally vitamin K2 is synthesized by intestinal bacteria especially *Escherichia coli* and *Bacteroides* species. The exogenous source mainly fulfils the vitamin K requirements though the body has a store for 5 weeks. But once the endogenous supply is depleted, and there is suppression of the intestinal flora by antibiotics, the prothrombin level falls¹, leading to haemorrhage especially in seriously ill patients.²⁻⁵ It has been suggested by experiments that methylthiotetrazole side chain containing antibiotics are responsible for the hypoprothrombinaemia.⁶ Other workers have provided evidence of impairment of post-translational processing of prothrombin by the methylthiotetrazole containing antibiotics.⁷ This was found in patients treated with cefamandole or moxalactam where descarboxyprothrombin was detected in the serum by agar gel immunoelectrophoresis. Small controlled studies on patients receiving antibiotics with the methylthiotetrazole ring have been performed to ascertain the incidence of coagulopathy. In one of these studies on patients with pneumonia, hypoprothrombinaemia occurred in 14 of 59 patients treated with moxalactam whereas only one of 54 patients receiving ceftizoxime and 2 of 56 patients on cefotaxime developed hypoprothrombinaemia. In a study involving patients with renal insufficiency, hypoprothrombinaemia occurred in 18 of 28 patients treated with a dose of 1 to 4 grams every 12 hours. The effect was noted after 4 days of initiation of therapy with the prothrombin time being prolonged by 18.3 seconds on an average. Two cases had bleeding in the form of haematemesis which was arrested with infusion of fresh frozen plasma, 14 were treated with a single subcutaneous injection of vitamin K and the prothrombin time was normalized within 36 hours. In 2 cases, the prothrombin levels returned to normal after discontinuation of cefoperazone. In this study hypoalbuminaemia was a constant factor (and this is a marker of the nutritional status) it could be presumed that the hepatic stores of vitamin K were already depleted. It was thus concluded that drugs containing the methylthiotetrazole structure are likely to cause prolongation of the prothrombin time. Platelet aggregation is the basis of primary haemostasis. This takes place in several phases and involves factors as Von Willebrand's factor, ADP and thromboxane A₂. Antibiotics have been found to impair platelet function, the mechanism of which has been studied in vitro.⁸ Prolongation of the template bleeding time is the clue to impaired platelet function.⁹ Beta-lactam antibiotics as ticarcillin¹⁰, nafcillin¹¹ and moxalactam^{12,13} are known to have caused haemorrhage due to a functional platelet defect. It was noted that the bleeding time is often markedly prolonged and this is dose dependent and that, drugs, having an alpha-carboxyl group adjacent to the beta-lactam ring as ticarcillin and moxalactam, cause prolongation of the template bleeding time. Other studies with antibiotics lacking the alpha-carboxyl marker as mezlocillin,¹⁴ piperacillin¹⁵ and apalcillin¹⁶ showed lower incidence of adverse effects on platelet function - The third generation cephalosporins other than moxalactam, such as cefotaxime, cefoperazone, ceftizoxime and ceftriaxone rarely impair platelet function. The interference in haemostasis by more than one pathway

by moxalactam has made it known to be a high risk for bleeding. Drugs interfering with either the vitamin K coagulation factors or platelet aggregation should be used cautiously as a concomitant therapy with anticoagulants, salicylates and nonsteroidal anti-inflammatory agents. It is also advisable to prescribe antibiotics carefully in patients suffering from hepatic cirrhosis, uraemia and thrombocytopenia. To combat the side effects of hypoprothrombinaemia without apparent bleeding, a single subcutaneous injection of vitamin K — 10 mg is sufficient. This brings the prothrombin time to the base line in a few hours; If hypoprothrombinaemia is secondary to a drug with a methylthiotetrazole substitution, a time period of 24 to 36 hours are required to bring the prothrombin level to normal limits after treatment with vitamin K. ¹⁷ If in this interval active bleeding ensues, then fresh frozen plasma should be transfused. If haemorrhage occurs due to prolongation of the template bleeding time, then platelet concentrates should be administered. Finally, as a rule of safety, antibiotics should be prescribed after considering the presence of factors which could lead to impairment of haemostasis.

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