Life threatening interaction between tamoxifen and warfarin

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Lodwick *et al* reported a life threatening interaction between tamoxifen and warfarin.[1] We report a retrospective study of similar cases in our hospital.

Case reports

A 43 year old woman started anticoagulant treatment with warfarin for a deep venous thrombosis. After a loading dose of 25 mg over three days she was given 5 mg daily, which maintained her prothrombin time at 19 seconds. Seven weeks later tamoxifen 40 mg daily was added to her treatment. The next day her prothrombin time was 38 seconds, and eventually she was restabilised on 1 mg warfarin daily to maintain a prothrombin time of 20-25 seconds.

This considerably reduced requirement for warfarin prompted a retrospective review of medical records at our hospital for the period 1981-6 to examine whether there might be an interaction between tamoxifen and warfarin. The records of women with breast cancer and a subsequent admission for a serious thromboembolism were examined. There were 18 such women: seven who had had deep venous thrombosis and 11 who had had a pulmonary embolus with probable deep venous thrombosis. Five of them were taking tamoxifen when they started taking warfarin. Two of them had complications after loading doses of warfarin: in one the prothrombin time after three daily doses of warfarin (10 mg, 10 mg, and 5 mg) rose to 50 seconds, and she developed a left subdural haematoma requiring warfarin to be withdrawn; in the other a similar loading dose regimen resulted in a prothrombin time of 49 seconds on day 7, the patient developed severe haematuria, and her anticoagulant treatment was changed to phenindione. The three other patients taking tamoxifen required daily doses of 2 mg, 2 mg, and 3 mg to maintain appropriate prothrombin times.

The dose of warfarin that maintained appropriate prothrombin times in the 13 patients not taking tamoxifen varied from 4 to 10 mg (mean 6·25 mg) daily. None of these patients had complications in the first month of treatment with warfarin.

Comment

Our observations suggest that women with breast cancer requiring warfarin need a lower dose if they are taking tamoxifen. The mechanism of the interaction between the two drugs is unclear, but protein binding and competition for metabolic pathways may both play a part. Both warfarin and tamoxifen are metabolised by the microsomal enzyme systems in the liver. Warfarin is a racemic mixture and the (S) isomer is four to five times more physiologically active than the (R) isomer. This more active (S) isomer is converted to the 7-hydroxy metabolite, which is inactive, by the cytochrome P450 enzyme system.[2] Three metabolites have been detected in the serum of patients taking tamoxifen. Normally tamoxifen accounts for 36% of the drug and metabolites present, desmethyltamoxifen for 58%, metabolite Y for 4%, and 4-hydroxytamoxifen for 1·5%.[3] All of these metabolites have some affinity for the oestrogen receptor, but the affinity of the 4-hydroxy metabolite is 50-100 times greater than that of the parent drug.[4] Accordingly, 4-hydroxytamoxifen is about 100 times more potent than tamoxifen in inhibiting the growth of MCF7 breast cancer cells in culture.[5]

The hydroxylations are probably carried out by similar enzyme systems. In the case of warfarin competition for the enzymes may increase the concentration of the active parent drug and decrease the concentration of inactive metabolites. In the case of tamoxifen, however, the resultant changes in the amounts of metabolites present may have important implications for the activity of the drug. Altering the percentage of the 4-hydroxy metabolite present may have an effect on the response of the tumour.

The hazards of an increased pharmacological effect of warfarin and a theoretically decreased antitumour effect of tamoxifen make this a potentially serious drug interaction, which warrants further investigation.

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Gastric explosion: a cautionary tale

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Gases in the colon will support combustion, and serious accidents have been reported when diathermy has been used for fulgurating colonic polyps.[1] Cutting diathermy is often used for enterotomy in surgery on the stomach and small bowel and has been considered safe. We found, however, that under certain circumstances gases in the stomach may be explosive.

Case report

An 82 year old man with carcinoma of the gastric antrum proved by biopsy had a laparotomy under general anaesthesia. A rapid sequence induction technique was used to avoid gastric distension, and anaesthesia was maintained with 70% nitrous oxide, 30% oxygen, and 0·75% halothane. At laparotomy the stomach was moderately dilated owing to an extensive and inoperable carcinoma of the gastric antrum and pylorus. A large bore nasogastric tube was inserted and the stomach contents aspirated, though the tube soon became blocked by gastric debris. Cutting diathermy was used for the gastrotomy during a palliative antecolonic gastrojejunostomy. As the stomach was opened the gases within it ignited momentarily, an explosion was heard, and the scrub nurse and the theatre light were sprayed with gastric contents. The stomach was carefully inspected but seemed unharmed. The operation was continued, and the patient subsequently made an uneventful recovery.

Comment

We were not previously aware that gaseous gastric contents might support combustion, though one case has been reported.[2] Initially we thought that