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(10 mg, 10 mg, and 5 mg) rose to 50 seconds, and she developed a left subdural haematoma requiring warfarin to be withdrawn; in the other a similar loading dose regimen resulted in a prothrombin time of 49 seconds on day 7, the patient developed severe haematuria, and her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 antecolic 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

anaesthetic gases had entered the stomach and caused this accident. Experiments have shown, however, that halothane of less than 7% concentration in 70% nitrous oxide with 30% oxygen cannot be ignited by a power source of 80-120 J, which is much greater than that used in surgical diathermy (10 J).³ The presence of other gases, such as hydrogen and methane, would make an explosion possible. We postulate that fermentation can occur in an obstructed stomach and produce explosive mixtures.

We report this case to make surgeons aware that explosive gases may accumulate in the stomach when the gastric outlet is obstructed. Before operation we were unaware of the extent of the obstruction in this patient. We recommend that an obstructed stomach be

completely emptied through a wide bore nasogastric tube either before or during surgery before cutting diathermy is used for gastrotomy. Alternatively, cutting diathermy could be avoided when the gastric outlet is obstructed.

We thank Mr J L Wilkins for permission to describe this case.

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Ethnic differences in birth statistics from central Birmingham

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During preparation of a health profile for Central Birmingham Health Authority¹ a significantly raised postneonatal mortality was found among Afro-Caribbean babies compared with European babies. A higher stillbirth rate and perinatal mortality among Asian babies and a lower stillbirth rate and perinatal mortality among Afro-Caribbean babies were also noted, as has been reported by others.^{2,3} We report these findings.

Methods and results

Our analysis was based on information collected for the Birmingham births register of the university department of social medicine. This is one of few sources of data on births in the United Kingdom where the ethnic origin of both parents is recorded. The sample comprised all births to parents resident in Central Birmingham Health Authority during 1982-4 inclusive (total number 9880). This was the largest sample obtainable: data from before 1982 were not readily available owing to changes in local authority boundaries, and data from 1985 onwards were incomplete at the time of the study. For each birth the outcome at one year was classified as stillbirth; death in the first, second, third, or fourth week; or death in the remainder of the year. Each birth was classified according to the ethnic group of both parents as European (white), Asian (Indian, Pakistani, or Bangladeshi), Afro-Caribbean, oriental, or mixed (when the parents were of different ethnic origin). The last two categories were combined to form "others" as the numbers were small. Statistical analysis was by the χ^2 test with Yates's correction. Results for births among Asians and Afro-Caribbeans were independently compared with those among Europeans.

The table shows the results. The most notable finding was a significantly higher postneonatal mortality among Afro-Caribbean babies ($\chi^2=8.95$, $p<0.01$). Causes of death in the postneonatal period were identified as far as possible by examining death certificates. Twenty seven babies (out of 56) were registered as having died of the sudden infant death syndrome. Congenital abnormalities accounted for 13 deaths, respiratory and other infections for five, accidental deaths for three, and other causes for three. Five files could not be located.

Number of births in Central Birmingham Health Authority in 1982-4 by outcome and ethnic group. Figures in parentheses are mortality/1000 births*

	Ethnic group			
	European	Asian	Afro-Caribbean	Other
Total births	4597	3821	669	793
Live births	4561	3780	668	786
Stillbirths	36 (7.8)	41 (10.7)	1 (1.5)	7 (8.8)
Babies dying in first week of life	30 (6.6)	26 (6.9)	4 (6.0)	8 (10.2)
Perinatal mortality	66 (14.4)	67 (17.5)	5 (7.5)	15 (18.9)
Babies dying in second, third, and fourth weeks of life	8 (1.8)	5 (1.3)	2 (3.0)	1 (1.3)
Neonatal mortality	38 (8.3)	31 (8.2)	6 (9.0)	9 (11.5)
Postneonatal mortality	21 (4.6)	19 (5.0)	10 (15.0)†	6 (7.6)
Infant mortality	59 (12.9)	50 (13.2)	16 (24.0)‡	15 (19.1)

*Mortality expressed per 1000 live births except for stillbirth and perinatal mortality rates, which are expressed per 1000 total births.

† $\chi^2=8.95$, $0.001<p<0.01$.

‡ $\chi^2=4.71$, $0.02<p<0.05$.

Comment

Increased postneonatal mortality and an increased incidence of the sudden infant death syndrome in Afro-Caribbean babies have been reported in America⁴ but not in Britain. Data on ethnic origin are not routinely collected when births are registered in Britain, and it is therefore unlikely that such a difference would be detected unless looked for specifically. Other districts that we contacted could not give any indication of this trend. Reasons suggested for an increased postneonatal mortality among Afro-Caribbeans include a different socioeconomic distribution from that among other ethnic groups and a lower mean birth weight.⁴ In our sample 387 (58%) Afro-Caribbean babies and 2363 (62%) Asian babies were born to parents in social class IV, V, or unclassified compared with 1444 (31%) European babies. Afro-Caribbean babies also had a different birthweight distribution, with 24 (3.6%) babies weighing less than 1500 g compared with 38 (1%) Asian babies and 58 (1.3%) European babies. This high incidence of very low birth weight babies among Afro-Caribbeans agrees with the findings of another study in Birmingham.⁵

The low perinatal mortality among Afro-Caribbeans in our study is largely attributable to the low stillbirth rate, although this value was based on small numbers and was not significant. Other studies from Britain³ and America,⁵ however, have shown Afro-Caribbeans to have low stillbirth rates and neonatal mortality specific to birth weight. We report this high postneonatal mortality in Afro-Caribbeans in the hope that others will review their birth statistics to see whether ethnic differences in postneonatal mortality exist.