Agranulocytosis caused by spironolactone

Spironolactone has been in widespread use for over 20 years, and so far as we know it has never been documented unequivocally as the cause of agranulocytosis. In only one report was the possible association mentioned briefly, and no details were given.1 The manufacturer has received a few reports of agranulocytosis over the years but in none was a causal role of spironolactone convincing (H van der Hulst, Searle Pharmaceuticals, personal communication, 1984). We have observed a patient in whom complete agranulocytosis was induced by spironolactone on two occasions.

Case report

A 70 year old woman was admitted for cardiac failure and renal dysfunction. On admission she had dyspnoea, chest pain on exertion, peripheral oedema, and hepatomegaly. She had not been using any medicines. Abnormal haematological findings were: urea concentration 22.4 mmol/l (135 mg/100 ml) (normal <7.5 mmol/l); <45 mg/100 ml); creatinine concentration 162 μmol/l (1.8 mg/100 ml) (normal <110 μmol/l; <1.2 mg/100 ml); γ-glutamyltransferase activity 88 IU/l (normal <40 IU/l); alanine aminotransferase activity 36 IU/l (normal <30 IU/l); lactate dehydrogenase activity 550 IU/l (normal <320 IU/l); Leucocyte counts were repeatedly normal with normal differentiation. Electrocardiography showed multiple ventricular extrasystoles. X ray film of the chest disclosed cardiomegaly and pulmonary congestion.

Treatment was instituted with digoxin 0.5 mg, frusemide 80 mg, and triamterene 50 mg daily and a sodium and protein restricted diet. She showed slow but definite improvement and digoxin and frusemide were decreased to 0.125 and 40 mg daily. Renal function remained impaired. Because of hyperkalaemia triamterene was discontinued. Once the serum potassium concentration had returned to normal spironolactone 100 mg daily was instituted (see figure). Five weeks later a routine blood count disclosed leucopenia (2·6 x 10^9/l) with complete agranulocytosis, relative lymphocytosis, and eosinophilia (15%). Bone marrow biopsy showed normal red cell and platelet production but many immature myelocytes in the absence of mature granulocytes. Spironolactone was discontinued. Within one week the granulocyte count was normal (4·1 x 10^9/l; 7% neutrophils) and two weeks later she was discharged.

One month after discharge the patient was readmitted because of dyspnoea and peripheral oedema. Frusemide was increased to 80 mg daily and digoxin to 0·25 mg daily and the importance of the diet re-emphasised. All signs and symptoms of congestive heart failure disappeared. Leucocyte counts were repeatedly normal. Renal function remained stable and the patient was discharged again. Two months later she was admitted for the third time. She had the same symptoms as before. In addition to her treatment regimen, which she had adhered to, she was again given spironolactone (50 mg/day). Three weeks later the leucocyte count (normal on admission and with normal differentiation) had fallen to 1·6 x 10^9/l. Differentiation showed complete agranulocytosis. The causal relation between spironolactone and the agranulocytosis was then recognised and the drug discontinued. Nine days later the leucocyte count was 4·5 x 10^9/l and showed normal differentiation.

Comment

In our opinion there is no doubt that spironolactone caused the agranulocytosis in this patient. All other drugs were continued without difficulty and no other cause was found. The temporal relation with the administration of spironolactone was clear on both occasions (see figure). In view of the apparent rarity of the reaction it may be idiosyncratic. Probably the mechanism is immunologically and acts by destroying granulocytes in the peripheral blood. The complete absence of granulocytes in the presence of many myelocytes in the bone marrow, the accelerated reaction to rechallenge, and the rapid and complete recovery after discontinuation of spironolactone on both occasions were compatible with a drug dependent antibody mediated reaction. Even common drugs that have been used safely for years may unexpectedly cause life threatening adverse effects. Plainly drug monitoring should not be restricted to new drugs only.

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Relation between use of tampons and urogenital carriage of group B streptococci

Although infection with group B streptococci in man was described in 1943, these bacteria were unfamiliar to clinicians until their association with neonatal infection was established in the 1960s.1 The reason for this apparent increase in the incidence of infections due to group B streptococci remains obscure. In the study reported here we found a positive correlation between the use of tampons and the carriage of group B streptococci, which might have contributed to the increase.
Patients, methods, and results

From November 1979 to June 1980, 143 pregnant women who were carriers of group B streptococci participated in a study of neonatal infections. Urine and cervical specimens were collected from the women at 36 weeks' gestation and at delivery. From October 1982 to March 1983, 104 (73%) of these women agreed to participate in the present study. The final study group consisted of 88 women (16 were excluded because of recent antibiotic treatment). Specimens were obtained from the urethra and cervix of the 88 women on two occasions t o six weeks apart. Culturing, identification, grouping, and typing of group B streptococci were performed as described elsewhere. 1-4 The strains isolated during 1979-80 were retyped together with the new isolates. Group B streptococci were isolated from 53 of the 88 women, all of whom had been carriers three years before the present study. The table shows that a positive correlation was found between persistent carriage and the use of tampons. Thus 38 (75%) of the women who used tampons were still positive for group B streptococci after three years compared with 15 (41%) of the women who never used tampons (p<0.01).

Relation of tampon use during menstruation to urogenital carriage of group B streptococci in 88 women who had been carriers* during pregnancy and delivery three years previously. (Figures are numbers (% of women)

<table>
<thead>
<tr>
<th>Tampon users (n = 51)</th>
<th>Non-users (n = 37)</th>
<th>p value^t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier of same type of group B streptococci</td>
<td>25 (49)</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Carrier of another type</td>
<td>13 (25)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>All carriers</td>
<td>38 (75)</td>
<td>15 (41)</td>
</tr>
</tbody>
</table>

*Patients were considered to be carriers when group B streptococci were isolated at one or both cultures.
^t y^ test with Yates's correction.

The type of group B streptococci isolated in 1982-3 was the same as that isolated in 1979-80 in 25 (49%) of the women who used tampons compared with nine (24%) of those who did not (p<0.05). Among the women who used tampons, 49% carried the same type of group B streptococci from 1982 to 1983 as from 1979 to 1980 compared to 24% who did not use tampons (p<0.05). The respective figures for cervical carriage alone (at one or both cultures) were 23 (45%) and seven (19%) (p<0.05). There was no difference in the proportion of women acquiring a new type of group B streptococci between the two groups (table). Furthermore, the distribution of types was similar between women who used tampons and those who did not.

The contraceptive methods used by the women were: intrauterine device (48%), barrier methods (27%), and oral contraception (25%). Of the specimens, 19% were collected during menstruation, 36% in the proliferation phase, and 43% during the secretion phase. None of these variables correlated with persistent carriage of group B streptococci or use of tampons, and there was no difference in age or parity between women who used tampons and women who did not.

Comment

The results show that prolonged carriage of group B streptococci in women who used tampons during menstruation was twice that in women who did not (49% v 24%). A causal relation between use of tampons and persistence of group B streptococci in the urogenital tract seems to be the most plausible explanation because those who used tampons did not differ from non-users with respect to age, parity, contraceptive method, or time of collection of specimens in relation to the menstrual cycle.

The use of tampons has been strongly related to the toxic shock syndrome, which is caused by Staphylococcus aureus. Furthermore, tampons cause vaginal and cervical ulceraions, which might have an infectious aetiology. Studies of the toxic shock syndrome indicated that tampons lead to an increase in the number of staphylococci in the vagina. A similar mechanism might result in the persistence of group B streptococci in the urogenital tract.

We suggest that the introduction of tampons might have caused an increased prevalence of carriage of group B streptococci in women, which may have led to more neonatal infections due to group B streptococci.

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Type A behaviour and heart disease prevalent in men in the Caerphilly study

Type A behaviour was associated with a twofold increase in incident ischaemic heart disease in two American studies. 1 The relation between type A behaviour and ischaemic heart disease in Britain, however, is unknown. We therefore report a cross sectional study of 711 men from Caerphilly, south Wales. 2

Subjects, methods, and results

A random sample of male electors aged 30-59 was invited to attend a local clinic. The London School of Hygiene chest pain questionnaire was administered and a 12 lead electrocardiogram recorded. Ischaemic heart disease was diagnosed if there were symptoms of angina, a history of myocardial infarction, or electrocardiographic evidence of myocardial ischaemia. 3 The last five items of the full 10 item Framingham type A scale were also administered, these items being selected as most relevant to this population. Type A questions relating to occupation were asked about current job or, for unemployed men, most recent job.

Of the 797 men eligible for inclusion in the study, 711 (89%) were examined. Of these, 565 were employed and type A scores obtained for 558. A preliminary analysis of type A score by employment state showed employed men to score higher than retired men but lower than men who were disabled or seeking work (Kruskall-Wallis test, p<0.05); hence the groups were not pooled. As the unemployed groups were too small to analyse separately, the table gives the mean type A scores in various categories of ischaemic heart disease and age for employed men only. Type A scores decreased with age and were slightly raised for men with ischaemic heart disease. When each disease category was examined a consistent relation with type A behaviour over all age categories was found for angina only (Mann-Whitney U test corrected for ties, p<0.01).

Comment

Although a high response rate was obtained, these data have several limitations. Firstly, a modified version of a validated question-