Prothrombin values after withdrawal of disopyramide and their response to warfarin

Day:	1 (disopyramide stopped)	2	3	4	5	6	7	8	9
Warfarin dose (mg) ..	3	3	5	5	6	5	6	8	6
Prothrombin time (s)..	24		16	15			19	22	28

warfarin might be explained by a competitive phenomenon at the receptor site if disopyramide is metabolised at the same site.

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Department of General Medicine, Walton Hospital, Liverpool L9 1AE
E HAWORTH, MRCP, medical registrar
A K BURROUGHS, MB, CHB, house physician

Pleurisy and methotrexate treatment

The association between adverse pulmonary reactions to cytotoxic agents such as busulphan, cyclophosphamide, and methotrexate is now well documented.[1] A syndrome of cough, dyspnoea, fever, and diffuse pulmonary infiltration has been described both in children with acute leukaemia[2] and in patients with psoriasis[3] on maintenance treatment with methotrexate. We wish to report the occurrence of pleuritis in patients treated with methotrexate for trophoblastic tumours, since this complication has not been a notable feature of reviews on the subject.[3 4]

Patients

We studied patients with trophoblastic tumours who were attending the medical oncology department at Charing Cross Hospital. Between 1958 and 1975, 317 patients were successfully treated with drug regimens including 50 mg methotrexate given as a single intramuscular dose, followed after 30 hours by folinic acid. This treatment was repeated to a total of 120 mg in eight days. Of these patients, 20 (6%) developed pleurisy. We excluded six of the 20 patients who had clear evidence of pulmonary metastases, from the series studied. The remaining 14 patients had no evidence of pulmonary disease or metastases but developed pleuritic chest pain, which occurred in association with the first treatment in some and up to the fifth in others (see table), but not necessarily with every course of treatment. In all but one of the patients studied the human chorionic gonadotrophin concentration was abnormally high when pleuritic pain developed. No patient had pleuritic pain associated with use of other cytotoxic agents. The eosinophil counts remained normal in all patients. In four there was radiological evidence of pleural effusion or basal shadowing compatible with localised collapse of lung. Pulmonary disease was not subsequently detected in any patient.

Comment

Treatment with methotrexate was associated with an acute pleural reaction in 20 of 317 patients with choriocarcinoma—an incidence of 6%. This relatively common and disturbing side effect has not been reported. It appeared to be directly associated with treatment, occurring immediately after administration of methotrexate; it is not clear why it occurred in some patients during the first course of treatment and in others after several treatments, nor why only some patients were affected. We have found that pleuritic pain does not occur in patients with pulmonary metastases from breast cancer treated with smaller doses of methotrexate, and that it is not apparently associated with intermittent high-dose (>200 mg) intravenous methotrexate in patients with trophoblastic tumours.

Association of development of pleurisy with course of treatment of methotrexate and folinic acid in patients with trophoblastic tumours, but without radiological evidence of metastases

Patient No	Course of treatment (No)	HCG concentration
1	5	Abnormal
2	5	Normal
3	2	Abnormal
4	2	Abnormal
5	2	Abnormal
6	4	Abnormal
7	2	Abnormal
8	3	Abnormal
9	3	Abnormal
10	2	Abnormal
11	5	Abnormal
12	3	Abnormal
13	2	Abnormal
14	3	Abnormal

HCG = human chorionic gonadotrophin.

The immediate association with treatment suggests a hypersensitivity response, but there was no eosinophilia, leucocytosis, wheezing, or rash in any of our patients. The pleural reaction may be associated with necrosis of tumour deposits on the pleura; this does not explain, however, the absence of pleural reaction to other cytotoxic agents which may be equally effective in reducing trophoblastic tumour mass. Trophoblastic embolism after treatment might be responsible for the pleural reaction,[4] but there is little evidence of pulmonary embolism in connection with methotrexate treatment.[5] Methotrexate may have a harmful effect on serosal cells lining the pleura or peritoneum.

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Department of Medical Oncology, Charing Cross Hospital, London W6 8RF
P A M WALDEN, MB, MRCP, senior registrar, department of medical oncology
P F MITCHELL-HEGGS, PHD, MRCP, lecturer in medicine
C COPPIN, MB, MRCP, senior house officer, department of medical oncology
J DENT, SRN, research assistant
K D BAGSHAWE, MD, FRCP, professor of medical oncology