COMBINATION CHEMOTHERAPY WITH C.I.S.-DIAMMINE-DICHLORO-PLATINUM, VINBLASTINE, AND BLEOMYCIN IN ADVANCED TESTICULAR NON-SEMINOMA

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Summary

40 patients with disseminated testicular non-seminoma were treated with cis-diammine-dichloro-platinum, vinblastine, and bleomycin. Complete remission was achieved in 24 (60%) patients and partial remission in 11 (28%). 22 of the 24 complete responders, who have been followed-up for a median of 11 months, have been tumour-free for 5–30 months. There were 3 drug-related deaths. This regimen is the most effective remission-induction treatment available for disseminated testicular non-seminoma. Patients should be treated in centres experienced in the specialised management of this potentially curable disease.

Introduction

Testicular neoplasms are rare, their annual incidence ranging from 0.9 to 4.5 per 100,000 males in Europe, and they occur most commonly in the 20–40 year age-group. They are the main cause of cancer death in men aged 25–34 years.1,2 Seminomas and non-seminomas comprise 85–95% of all testicular tumours.3,4 When seminomas are treated by radiotherapy to the regional lymph-nodes after orchietomy the cure-rate is 90–95%.4,5 Until recently, the prognosis of disseminated non-seminoma was very poor. Combination chemotherapy with actinomycin-D, methotrexate, and chlorambucil resulted in 10–20% complete remissions.6–9 These results were improved when Samuels introduced vinblastine (V.L.B.) and bleomycin (B.L.M.) and obtained complete remissions in 39% and partial remissions in 35% of a series of consecutive cases.10–12 The encouraging results obtained with cis-diammine-dichloro-platinum (C.D.D.P.)13–18 in phase I19,20 and phase II21,22 studies in testicular non-seminoma led to its use in combination chemotherapy. In 1976 Einhorn reported the first results of C.D.D.P., V.L.B., and B.L.M. remission-induction therapy,23 followed by maintenance on V.L.B. and B.C.G. immunotherapy. The promising results were subsequently confirmed, and in 1978 he reported 33 (70%) complete and 14 (30%) partial remissions in 47 patients. 27 patients were still in complete remission after a follow-up of 26–49 months.24–26 Better remission-rates were not obtained by adding other drugs to this combination.27–30

In June, 1976, we started a study of C.D.D.P., V.L.B., and B.L.M. in patients with stage III non-seminoma. The maintenance therapy consists of C.D.D.P. and V.L.B., scheduled for 2 years.

Patients and Methods

40 patients, aged 17–53 years (mean 32 and median 29), with disseminated testicular non-seminoma have been given remission-induction chemotherapy consisting of C.D.D.P., V.L.B., and B.L.M. All patients had measurable lesions except 1 in whom a raised serum-level of the β-subunit of human chorionic gonadotrophin (β-H.C.G.) was the sole indicator. The patients were classified according to Pugh (table I). The extent of spread of metastases was assessed according to Samuels.11 Table I shows that most of the patients had advanced abdominal and/or advanced pulmonary disease. 50% of them had previously been treated with radiation and/or chemotherapy for metastases; these included 2 who had received V.L.B. and B.L.M. and 1 who had received V.L.B. and B.L.M. followed by C.D.D.P., Adriamycin (doxorubicin), and cyclophosphamide.

After prehydration with 1 litre of saline, C.D.D.P., 20 mg/m² in 300 ml 15% mannitol, was infused over 2 h for 5 consecutive days. Three to four cycles were given, the next cycle starting on day 22 of the previous cycle. During each treatment cycle, diuresis was maintained by at least 4 litres of saline/24 h. V.L.B. was given as an intravenous bolus on days 1 and 2 of each treatment cycle in a dose of 0.2 mg/kg daily. B.L.M. 30 U intravenously was given in a 15 min infusion 6 h after the V.L.B. on day 2 of each cycle and also at weekly intervals between cycles until a total dose of 360 U had been given. The sequential use of V.L.B. and B.L.M. is based on experimental data obtained in cell-cycle kinetic studies and animal models.31,32

After remission-induction chemotherapy complete responders were maintained on intravenous V.L.B. (0.3 mg/kg), alternating with intravenous V.L.B. (0.2 mg/kg) plus intravenous C.D.D.P. (50 mg/m²) at 3 week intervals for 2 years. Patients were admitted for 1 day every 6 weeks for the C.D.D.P.-V.L.B. combination. The C.D.D.P. was provided by the

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National Cancer Institute, National Institutes of Health, Bethesda, Maryland, U.S.A.

Complete remission was defined as complete disappearance for at least 8 weeks of all clinical, radiographic, and biochemical evidence of disease, which included the results of whole-lung tomography, computerised tomographic scanning of the abdomen, exploratory surgery if indicated, and assays of β-H.C.G. and α-fetoprotein (A.F.P.). Partial remission was defined as a decrease of 50% or more in the sum of the products of the perpendicular diameters of all measurable lesions for at least 8 weeks. If the disease progressed under this regimen, the case was classified as one of "progression" and the patient was excluded from the study.

Results

24 (60%) of the 40 patients achieved complete remission, 11 (28%) patients achieved partial remission, and 3 patients died of toxicity (table I). 2 of the 3 deaths occurred during remission-induction treatment; 1 was due to agranulocytic sepsis and the other to myocardial infarction (box below). The third patient died of B.L.M. lung fibrosis 6 months after completion of remission-induction chemotherapy, when he was still in complete remission. The lung fibrosis had developed when he was still on B.L.M. 2 other patients, who showed enlargement of lung metastases during remission-induction treatment, were classified as cases of progression and dropped from the study.

22 of the 24 complete responders, who have been followed-up for an average of 13 months (median 11 months), have remained disease-free for 5–30 months. 1 of the other 2 patients showed recurrence of the disease after 7 months of complete remission: the recurrence was accompanied by a rise of lactate dehydrogenase (L.D.H.) and β-H.C.G. levels. At laparotomy, retroperi-

toneal lymph-node metastases were found. After irradiation of these metastases, the level of tumour markers became normal. The other patient was operated on, after 2 cycles of remission-induction chemotherapy, to reduce the size of a large differentiated teratoma in the abdomen, which recurred after 6 months of complete remission.

7 of the 11 partial responders showed progression of the disease after 3–5 months. 4 patients are still in partial remission after a follow-up of 6–15 months. Poor prognosis seems related primarily to the extent of the disease (table II). The preponderance of patients with advanced pulmonary and advanced abdominal disease is

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>No. of patients with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M.T.I.</td>
</tr>
<tr>
<td>Minimum pulm. disease</td>
<td>1</td>
</tr>
<tr>
<td>Advanced pulm. disease</td>
<td>3</td>
</tr>
<tr>
<td>Minimal abd. pulm. disease</td>
<td>0</td>
</tr>
<tr>
<td>β-H.C.G. as sole indicator</td>
<td>5</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>9</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Tumour markers*</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Positive</td>
</tr>
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<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td>Minimum pulm. disease</td>
<td>2</td>
</tr>
<tr>
<td>Advanced pulm. disease</td>
<td>16</td>
</tr>
<tr>
<td>Minimal abd. pulm. disease</td>
<td>1</td>
</tr>
<tr>
<td>Advanced abd. disease</td>
<td>20</td>
</tr>
<tr>
<td>β-H.C.G. as sole indicator</td>
<td>1</td>
</tr>
</tbody>
</table>

* Markers are considered positive when β-H.C.G. is > 4 ng/ml and/or A.F.P. is > 16 ng/ml.

striking; those with advanced abdominal disease have the worst prognosis.

None of the histological types showed a preponderance of advanced disease (table III). In 30 (75%) patients, tumour markers such as β-H.C.G. and/or A.F.P. were present. The presence of tumour markers was commoner in patients with advanced abdominal disease than in patients with advanced pulmonary disease (table IV).

Patients who had previously received radiotherapy were at greater risk of severe and prolonged haematological toxicity (table V). Septic shock and the treatment of sepsis with gentamicin and cephalothin contributed to the development of renal failure, which is a major side-effect of C.D.D.P. Of the 20 patients who had been treated previously, only 9 (45%) achieved a complete remission, compared with 16 (80%) out of 20 in the non-pretreated patients. The poorer prognosis in patients with radiotherapy was partially due to an increase in the number and severity of side-effects of chemotherapy, which can be reduced by decreasing the V.L.B. dose.
TABLE V—SIDE-EFFECTS OF CHEMOTHERAPY IN RELATION TO PREVIOUS THERAPY

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>No. of patients</th>
<th>R.T.±chemo</th>
<th>Chemo only</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=8)</td>
<td>(n=20)</td>
<td></td>
</tr>
<tr>
<td>Granulocytopenia†</td>
<td>15</td>
<td>10</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia‡</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>11</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure§</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*R.T.=radiotherapy; chemo.=chemotherapy.
†<5.0×10⁹ per litre for >5 days.
‡<50×10⁹ per litre for >5 days.
§Serum-creatinine >120 mmol/l.

19 patients were given four cycles of C.D.D.P., V.L.B., and B.L.M. In 12 complete responders the fourth cycle was intended as consolidation therapy, required because of the large size of the original tumour and/or excessively raised level of tumour markers present at the beginning of chemotherapy. The other 7 patients, who had only partial remission after three cycles, did not achieve complete remission with a fourth cycle.

Exploratory surgery was done in 17 patients during or after the completion of the chemotherapy to reduce tumour bulk (1 patient) and to assess response to treatment. Investigation of previously affected lymph-nodes by laparotomy was done in 13 patients and revealed fibrosis (5 patients), necrosis (2 patients), normal architecture (3 patients), benign differentiation of the tumour (1 patient), and a resectable polycystic necrotic mass with a diameter of 10 cm (1 patient). This last patient also had a large supraclavicular lymph-node swelling which showed fluctuation after two cycles of chemotherapy, and which at dissection appeared to be a polycystic necrotic tumour, 8 cm in diameter. However, histological examination showed intermediate malignant teratoma cells in the peripheral layer of both the abdominal and the supraclavicular masses. Neither of these tumours shrank during chemotherapy. The 13th patient was rendered disease-free by resection of a small residual retroperitoneal lymph-node metastasis after four cycles of chemotherapy (he is classified as a partial responder).

Exploratory thoracotomy was done in 3 patients after chemotherapy because of a solitary residual metastasis in 2 and a more than 50% reduction of pulmonary metastases in the third. The pulmonary metastases in this last patient consisted of differentiated and intermediate malignant teratoma. In 1 of the other 2 patients the lesion was a hamartoma; no residual tumour was demonstrated in the second. Dissection of a residual supraclavicular tumour disclosed fibrosis in the 17th patient.

Both of the patients previously treated with V.L.B.-B.L.M are now in complete remission, which has lasted 12 months. The patient pretreated with C.D.D.P.-cyclophosphamide-'Adriamycin' has had a partial remission for 3 months with impressive relief of severe pain.

TOXICITY

The side-effects of C.D.D.P. combination therapy have been described in detail.33–38 We present case-reports of 3 patients who died from complications of the combined C.D.D.P., V.L.B., and B.L.M. therapy.

Case 1

A 34-year-old man had a left-sided orchietomy (M.T.U. plus seminoma) and radiotherapy (4000 rad) to the regional lymph-nodes in 1976, followed by further radiotherapy 2 months later for a lung metastasis. 4 months later he was started on chemotherapy for a right hilar mass. Side-effects during the first cycle included vomiting, leucopenia, thrombocytopenia, stomatitis, and b.l.m.-induced fever.

With the second treatment cycle he had paralytic ileus, agranulocytosis, septic fever (although repeated blood-cultures were negative), and severe stomatitis (Candida albicans). He was treated with gentamicin and cephalothin and topical nystatin. Anuria developed; he was haemodialysed, and renal function recovered after 2 weeks. Meanwhile, severe diarrhoea developed and Candida albicans was cultured from the stools; he was then treated with intravenous miconazole.

His persistent fever, agranulocytosis, and anemia gradually improved with leucocyte and red-cell transfusions; his hearing loss, which occurred after treatment with gentamicin and cephalothin, disappeared; and the right hilar lung metastasis regressed.

The third and fourth treatment cycles had been delayed and was given in reduced doses. 6 months after the achievement of complete remission, he had dyspnoea, probably due to b.l.m. pneumonitis. B.L.M. was immediately withdrawn (by then the patient had received a total of 240 l). Prednisonone did not relieve symptoms. Subcutaneous emphysema and a pneumomediastinum developed, the lung infiltrates spread, and he died a week later of progressive respiratory insufficiency. Necropsy was refused.

Case 2

A 32-year-old man had a left-sided orchietomy (M.T.U. plus M.T.I.) in 1977. After 3 cycles of actinomycin-D (total dose 15 mg) a second-look laparotomy revealed progression of the disease and bulky retroperitoneal and liver metastases. When he was seen by us he also had lung metastases and impaired renal function due to left ureteric obstruction by a tumour. Reduced (75%) doses of C.D.D.P. and V.L.B. dosages were given; frusemide was also given because of fluid retention during the first treatment cycle. 3 days after discharge he was re-admitted because of septic shock (Enterobacter arogenes) which had been present at least 24 h. Despite intensive treatment, the patient died of irreversible shock. At necropsy, the lung metastases consisted solely of necrotic and fibrotic tissue, but viable tumour tissue was present in the retroperitoneal lymph-nodes.

Case 3

A 52-year-old man had a right-sided orchietomy (M.T.U.) and radiotherapy (4600 rad) to the regional lymph-nodes in 1977. 4 months later, he received chemotherapy for lung metastases. He also had hypertension. Because of his age and previous radiotherapy, the dose of C.D.D.P. and V.L.B. was reduced by 25%. The lesions regressed, but the first treatment cycle was complicated by severe myelosuppression, impairment of renal function, paralytic ileus, and sepsis (a temperature of 39.4°C but negative blood-cultures). The patient had myalgia, dizziness, and lethargy. He improved with co-trimoxazole, carbencillin, and red-cell and platelet transfusions, but lost 13 kg in the next 2 months. Despite further reduction of V.L.B. to 50% of the initial dose, the second, third, and fourth treatment cycles were all complicated by severe granulocytopenia, thrombocytopenia, and raised serum-creatinine levels. Hearing deteriorated. 1 week after the completion of remission-induction therapy, the patient was readmitted with agranulocytic
sepsis, pneumonia in the left lower lobe, hypocalcemia and hypomagnesemia (with tetany), and renal function impairment. He was given amikacin and carbencillin for a day, then placed on intravenous co-trimoxazole. He became febrile and the chest X-ray abnormalities disappeared, but he had to be haemodialysed because of renal failure. He began to have melena, which persisted despite repeated platelet transfusions. He died of a fatal arrhythmia due to myocardial infarction while on haemodialysis. At necropsy, all metastases had disappeared; there were also a myocardial scar and signs of an adjacent infarction, severely arteriosclerotic coronary arteries, renal tubular necrosis, and two gastric ulcers.

Other Cases

Some of our patients had other side effects—inability to taste, possibly due to zinc deficiency (7 patients), foul taste (9 patients), body odour (7 patients), and transient hoarseness (3 patients). All patients had nausea and vomiting, which seems to respond to metoclopramide.39 Weight-loss ranged from 5–13 kg in our patients at the end of remission-induction treatment. Although clinical neutropenia was seen in 27 patients, it is not clear whether it is due to V.L.B. or to C.D.D.P. Neutropenia affected only the sensory system except in 1 patient. 2 patients had C.D.D.P. allergy while on maintenance therapy; 1 had recurrent dermatitis after each C.D.D.P. administration, and the other had generalised urticaria followed by erythema and facial oedema. In both patients C.D.D.P. was withdrawn.

Discussion

There is agreement on the treatment of testicular seminomas, but none on that of non-seminoma. Although it is now widely accepted that stage II (metastases above the diaphragm or in abdominal visceral organs) should be treated with chemotherapy, some centres still irradiate solitary metastatic lung tumour. The treatment of stage II (metastases in the retroperitoneal lymph-nodes, with or without extension into the adjacent areolar tissue) is even more of a problem, since there is no clear-cut information on the effect of retroperitoneal lymph-node dissection, radiotherapy, or adjuvant chemotherapy. Factors that may influence the choice of treatment are the histological type of the tumour, the tumour load, and the presence of the tumour markers such as H.C.G. and A.F.P.2,14,42 The lack of agreement on the treatment of choice explains why those patients who had been previously treated had received different treatments. The remission-rate, although lower than that in Einhorn’s series,24 was high, particularly when the advanced stage of the disease in most of our patients is considered. Although the numbers are small, chemotherapy seems less effective in trophoblastic teratoma.

In September, 1978, Einhorn reported that 27 out of 33 complete responders remained in complete remission for 26–49 months.25 Patients who remain in complete remission for 2 years have been shown to have a life expectancy almost as good as that of age-matched healthy controls.1,15 In Einhorn’s series more than 50% of the original 47 patients treated with C.D.D.P., V.L.B., and B.L.M. have been in complete remission for more than 2 years and are probably cured. In our series it is still too early to assess long-term survival, since only 3 patients have completed 2 years of maintenance therapy.

Exploratory surgery has helped in the assessment of complete remission, since necrosis and fibrosis or benign differentiation can be detected only by histological examination especially in cases with residual tumour tissue in the abdomen.

The remission-induction regimen with C.D.D.P., V.L.B., and B.L.M. was very toxic, the most important side-effects being agranulocytic sepsis, renal failure, and B.L.M. lung fibrosis. The experience with case 1 shows that anaemia due to this combination of drugs may be reversible and should be treated by haemodialysis. The complication can usually be avoided by prehydration and forced diuresis, either by mannitol or saline.

Despite normal serum-creatinine levels, many patients become moderately hypernatremic and hypokalemic. Although we did not monitor serum-levels of magnesium, calcium, or trace metals in all of our patients, we found evidence of decreased levels in a number of them, possibly due to subclinical tubular damage. Monitoring for and supplementing these deficiencies are essential. Since the renal tubules are made vulnerable by C.D.D.P., the use of the potentially nephrotoxic antibiotics, gentamicin and cephalothin,44 and of the diuretic, frusemide, are45,46 should be avoided. If doses of co-trimoxazole are adjusted according to serum-levels of trimethoprim and sulphamethazine no deterioration of renal function will occur.47 One of the participating centres (Groningen) has used cephradine without observing nephrotoxicity. If the diuresis is less than 1 litre/6 h, a bolus of mannitol should be given. Our findings indicate that severe toxicity is more likely to occur in patients who have had previous radiotherapy and/or chemotherapy, those who are in an advanced stage of the disease, and possibly also those who are elderly. In such cases the V.L.B. dosage should be reduced by 25–50%.

This was not done at the time in many of the cases in this series, but it is our present approach. Supportive measures such as intestinal decongestion, intravenous hyperalimentation, and prophylactic co-trimoxazole (which has been shown to be effective in acute leukaemia48) may also help to prevent serious complications, but these need further investigation.

One of the centres (Utrecht) discharges patients on the day after the completion of a treatment cycle, but only after accurate instruction, which is very important in preventing delays in re-admission if fever develops at home.

It has recently become known that B.L.M.-treated patients have an increased risk of oxygen toxicity.49,50 This explains the rapid progression of the respiratory insufficiency in patient no. 1. In cases with respiratory insufficiency, oxygen therapy should be used with caution. During and after surgical procedures, the oxygen flow-rate should not exceed 20–25%. B.L.M. should be withdrawn when creatinine-clearance falls below 50 ml/min, because drug elimination is then severely impaired41,51—what is most probably happened in patient 1 on day 8 of the second treatment cycle.

C.D.D.P. allergy may become a commoner problem as this drug becomes used in prolonged maintenance treatment. We have been using C.D.D.P. and V.L.B. maintenance chemotherapy for more than a year now without coming across impairment of the renal function.

In view of the small numbers of patients with non-seminomatous testicular cancer and the relatively high
proportion of severe complications, we conclude that these patients should be treated in centres experienced in the complicated management of this often curable disease.

We thank Dr. P. H. J. Sleek and Dr. J. M. A. de Jong for their cooperation.

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CURE OF APLASTIC ANÉMIA IN PAROXYSMAL NOCTURNAL HÉMOGLOBINURIA BY MARROW TRANSFUSION FROM IDENTICAL TWIN: FAILURE OF PERIPHERAL-LEUCOCYTE TRANSFUSION TO CORRECT MARROW APLASIA

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Summary

The ability of syngeneic peripheral leucocytes to cure marrow aplasia was tested in a patient with paroxysmal nocturnal haemoglobinuria (p.N.H.). Transfusion of 7.1×10^10 white cells obtained by leucopheresis from an identical-twin donor, providing 3.4×10^4 myeloid progenitors (c.F.U.-c)/kg, failed to improve marrow function within two months. In contrast, transfusion of 1.3×10^10 nucleated bone-marrow cells, representing 6.4×10^4 c.F.U.-c/kg, from the same donor resulted in prompt bone-marrow recovery. These observations support the hypothesis that aplastic anemia in p.N.H. is a stem-cell defect that may be corrected by the simple infusion of relatively small numbers of normal bone-marrow cells. They also seem to indicate a distinct advantage of marrow cells over peripheral-blood mononuclear cells in their ability to correct marrow aplasia.

Introduction

In mice^1and dogs^2 aplastic bone-marrow can be repopulated by transfusion of pluripotent stem-cells obtained from peripheral blood. In man, the collection of large numbers of circulating normal leucocytes has been made possible by improvements in leucopheresis techniques. The feasibility of marrow repopulation by the transfusion of peripheral leucocytes is therefore of considerable practical, as well as theoretical, interest.

Referral of a patient with paroxysmal nocturnal haemoglobinuria (p.N.H.) and refractory bone-marrow failure who had a haematologically normal identical-twin sister gave us the opportunity to find out whether pluripotent haemopoietic stem-cells circulate in man and are capable of repopulating an empty bone-marrow. p.N.H. is a stem-cell disease that occasionally results in frank aplastic anemia. A previous report indicated that marrow aplasia in a patient with p.N.H. could be overcome with the infusion of relatively small numbers of normal bone-marrow cells from an identical twin. We have tested the ability of syngeneic peripheral leucocytes to cure marrow aplasia resulting from a stem-cell defect.

Case-report

A 24-year-old white woman was well until April, 1978, when she developed increasing dyspnoea, fatigue, and pallor. In July, 1978, she entered hospital with a haemoglobin level of 5.8 g/dl and white blood-cell (w.b.c.) count 1800/mm^3 with 35% neutrophils and 23 000/mm^3 platelets. The reticulocyte count was 2.3%. Coombs' test was negative. A sugar-water haemolysis test, Ham test, and haemosiderin staining of the urine sediment were positive. Serum iron and iron-binding capacity were normal. Leucocyte-alkaline-phosphatase score
was 10 (normal 50–150). A bone-marrow biopsy specimen was hypocellular with a few foci of erythroid precursors. No exposure to viral hepatitis, organic solvents, or other toxic compound was identified. She was transferred to U.C.L.A. Hospital for possible bone-marrow transplantation.

Physical examination revealed a pale, well-nourished young woman with multiple cutaneous and mucosal hemorrhages and without significant enlargement of lymph-nodes, spleen, or liver. Laboratory examinations included initial haemoglobin of 8.3 g/dl, w.b.c. 1400/mm³ with 17% segmented neutrophils, platelets 10 000/mm³, and reticulocytes 1.6%. Total serum bilirubin was 0.6–1.3 mg/dl, serum-lactate-dehydrogenase 260–419 u/l (normal 95–185 u/l), serum-iron 135 μg/dl, serum-iron-binding-capacity 256 μg/dl, and serum-haptoglobin less than 10 mg/dl. A serum-hepatitis-antigen screening test was negative. A Ham test was negative, but the sucrose-haemolysis test was positive on repeated examination. Gross haemoglobinuria was observed on several occasions. Bone-marrow biopsy showed an overall fatty marrow with patchy foci of cellularity composed primarily of erythroid precursor cells.

In her first ten days in hospital the patient had severe thrombocytopenia and profuse bleeding refractory to random donor platelets. 2–4 pints of blood were required weekly to maintain haemoglobin above 8 g/dl. After verification of complete identity with her prospective donor by comparison of red-cell antigens and isoenzymes and fingerprint patterns, an attempt was made to restore bone-marrow cellularity with repeated transfusion of her sister's leucocytes obtained by centrifugation leucopheresis (Hemonetics). Leucocyte-counts and differential counts were performed by standard techniques. Myeloid stem-cells (c.f.u.–c) were measured as previously described.7

A total of 7.08×10¹⁰ leucocytes, representing 3.4×10⁶ c.f.u.–c/kg recipient body-weight, were given over a period of fourteen days. In addition, platelet concentrates obtained by centrifugation and containing leucocytes were given repeatedly. Peripheral-blood platelet, total-w.b.c., and polymorphonuclear-leucocyte (P.M.N.) counts before and after these transfusions are shown in the accompanying figure. In contrast to the failure of random donor platelets to raise platelet-counts above 10 000/mm³, syngeneic donor platelets gave excellent transient increments in platelet-counts. However, no sustained increase in platelet, w.b.c., or P.M.N. counts was observed after these transfusions, and a repeat bone-marrow biopsy specimen showed no improvement in cellularity. Two months after w.b.c. transfusions were begun, haemoglobin was still 6.5 g/dl and w.b.c. 2100/mm³, with granulocytes 250/mm³, and platelet-count 6000/mm³. In view of the failure of leucocyte transfusions to improve marrow function, the same identical twin donated bone-marrow containing 1.28×10¹⁰ nucleated cells and 6.4×10⁴ c.f.u.–c/kg body-weight. This was transfused without any chemotherapeutic or radiotherapeutic conditioning regimen sixty-two days after w.b.c. transfusions were started. The first signs of bone-marrow recovery were observed fourteen days later, with a reticulocytosis of 6.6%, a slight increase in P.M.N. counts, and gradually increasing platelet-counts. Thereafter, peripheral-cell counts increased steadily and no more transfusions were required. By mid-January, ten weeks after bone-marrow transfusion, the haemoglobin was 13.1 g/dl, w.b.c. 3400/mm³ with 22% neutrophils and platelets 71 000/mm³. Bone-marrow examination revealed normal cellularity, and the sugar-water test and Ham test were negative.

Discussion

Although methods for the repopulation of haemopoietic tissues by transfusion of autologous or allogeneic bone-marrow cells are now well established, alternative procedures such as the use of peripheral-blood mononuclear cells for bone-marrow replenishment in man are still largely unexplored. Such a method would be of considerable advantage over the use of bone-marrow cells since (1) peripheral w.b.c. are much easier to obtain than bone-marrow cells; (2) repeated w.b.c. collection by leucopheresis can provide these cells in practically unlimited numbers; and (3) in patients with malignant disease and bone-marrow metastases, peripheral w.b.c. may still provide uncontaminated pluripotential stem-cells for autologous marrow reconstitution.

Experimental models of marrow aplasia induced by lethal-dose radiation in rodents and dogs have demonstrated that peripheral-blood leucocytes can repopulate the haemopoietic system at a dose of 2 to 14×10⁶ c.f.u.–c/kg body-weight.4 In man, large numbers of circulating w.b.c., with a total c.f.u.–c content equal to that of a bone-marrow harvest for transplantation, can be collected by currently available leucopheresis methods.8,9 However, there is no convincing clinical evidence that transfused normal w.b.c. can repopulate the bone-marrow. Accidental engraftment of transfused w.b.c. from chronic myelocytic leukaemic donors has been observed many times, and cryopreserved w.b.c. can be used for autologous marrow reconstitution in chronic myelocytic leukaemic patients with blastic transformation.10–12 Fatal graft-versus-host disease following the transfusion of granulocytes from normal donors has been reported,13,14 but there was no evidence of a simultaneous engraftment of haemopoietic tissues in these patients. A preliminary trial involving the transfusion of cryopreserved autologous peripheral mononuclear cells following intensive chemotherapy failed to accelerate haemopoietic recovery.15

The diagnosis of P.N.H. and aplastic anaemia in a patient with an identical-twin donor provided a unique setting in which to explore the ability of peripheral leucocytes to reconstitute syngeneic bone-marrow. Aplastic anaemia in P.N.H. is a stem-cell defect that is correctable by the transfusion of small amounts of genetically identical marrow stem-cells.6,16 However, the transfusion of peripheral leucocytes with a total c.f.u.–c content comparable to that given in marrow transplantation could be expected to be effective. Isologous w.b.c. transfusions in our patient, providing 5.8×10¹⁰ mononuclear leucocytes with 3.4×10⁶ c.f.u.–c/kg, resulted in no improvement in marrow cellularity or in peripheral-cell counts within two months. In contrast, clear evidence of marrow recovery was seen two weeks after the transfusion.
of 1.28×10^9 bone-marrow cells, with a C.F.U.-C content of 6.4×10^9/kg, from the same donor. These observations seem to indicate a distinct advantage of marrow cells over peripheral-blood leucocytes in their ability to correct marrow aplasia. Although a very late response to leucocyte transfusions in our patient cannot be ruled out, the prompt engraftment following marrow transfusion and the lack of any beneficial effect before such transfusion makes it unlikely.

This report does not rule out the potential therapeutic usefulness of autologous or isologous leucocytes in replenishing marrow cellularity in all patients; however, it demonstrates that with present leucopheresis technology, the amount and quality of pluripotent stem cells that can be harvested from the circulation of normal donors within a period of one to two weeks is not enough to ensure bone-marrow engraftment in all cases of haemopoietic stem-cell failure.

This work was supported by United States Public Health Service grant CA 15619.

Requests for reprints should be addressed to M.J.C.

REFERENCES


“In the area of morale, I believe it is up to our profession to give a lead by example even more than by precept, in condemning actions that harm patients; strangely unpopular though it may be to say so, we are privileged to be members of a great and honourable profession, and we must accept the responsibilities that go with that position. But even if we succeed in restoring high morale it will wither away in frustration unless the ability to take decisions at an appropriate level is recreated. The present structure allows decisions to be shelved, and creates confusion between those matters that are best decided locally and those that need to be decided centrally, since they are likely to be general in their effects. The general principle should surely be that whatever can be decided locally should be so decided, since the time taken to reach a decision is a function of the number of the decision-nodes that have to be surmounted. There is room for improvement in communications, remembering always that the most essential ingredient in proper communication is goodwill, to which technical devices are strictly ancillary.

No doubt times are bad; history suggests that perhaps they always were bad, for the great majority of people. The future of the health service depends on our recovering cheerfulness and dedication; the future of our own profession depends on a shared idealism, as William Stokes maintained over a century ago.”—Sir DOUGLAS BLACK JF R. Coll. Physns, 1979, 13, 57.

IMPROVEMENT IN IRON STATUS AND LIVER FUNCTION IN PATIENTS WITH TRANSFUSIONAL IRON OVERLOAD WITH LONG-TERM SUBCUTANEOUS DESFERRIOXAMINE

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Summary

Subcutaneous desferrioxamine (2–4 g over 12 h) was administered 6 nights each week to 34 patients with transfusional iron overloads who continued to receive regular blood-transfusions. All 34 patients showed a fall in serum-ferritin after 5 to 12 months. In some patients serum-ferritin fell almost to normal. Liver function improved in all the patients, serum-aspartate-transaminase levels fell in all 17 patients tested, and liver-iron fell in 5 of 6 patients tested. These studies show that body-iron stores can be substantially reduced, to normal or near normal levels, by long-term subcutaneous desferrioxamine in patients with transfusional iron overload despite the need for

![Fig. 1—Serum-ferritin in 34 patients before and 5–20 months after starting subcutaneous desferrioxamine therapy.](image-url)
continued blood-transfusion. They also show that removal of iron is accompanied by improved organ function.

**Introduction**

Regular subcutaneous desferrioxamine (D.F.X.) infusion therapy was suggested\(^1\) as a means of obtaining substantial iron excretion and preventing death from iron overload in patients receiving regular blood-transfusions for refractory anaemia such as beta-thalassaemia major. A number of studies\(^2,3\) have confirmed that up to 200 mg of iron may be excreted each day in the urine in iron-overloaded patients receiving 1-4 g of subcutaneous D.F.X. infusions each day over an 8-12 hour period. These excretion-rates, if maintained, should lead to substantial negative iron balance despite the continuing need for blood-transfusion. We have now treated a group of 34 patients with transfusional iron overload with subcutaneous D.F.X. for periods of 5-20 months. The results show a reduction in iron stores assessed by serum-ferritin in each case despite continued regular blood-transfusion. There has also been an improvement in liver function and a fall in liver-iron concentration.

**Patients and Methods**

34 patients—31 with beta-thalassaemia major (16 resident in Athens), 2 with sideroblastic anaemia (both women, aged 21 and 66), and 1 with pure red-cell aplasia (a woman aged 23)—have been studied. Among the thalassaemia patients, there were 21 males and 10 females aged 8 to 23 years, and they had received between 80 and 430 units of blood. None of the patients had previously received regular intramuscular D.F.X. for more than 1 year. The patients received 2-4 g D.F.X. by slow subcutaneous infusion over 12 h on 6 nights each week, and also vitamin C 200 mg daily orally separate from food. The optimum dose of D.F.X. for each patient was determined by urinary iron-excretion studies.

Before D.F.X. therapy was started, the following investigations were done: full blood-count, liver-function tests (including serum albumin, aspartate transaminase, alkaline phosphatase, and bilirubin), serum-iron, total iron-binding capacity, serum-ferritin,\(^4\) liver biopsy with estimation of liver-iron, echocardiography, and a number of endocrine investigations. The details of all the initial findings will be reported elsewhere.

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**LIVER-IRON CONCENTRATION, SERUM-FERRITIN, AND SERUM-ASPARTATE-TRANSAMINASE IN 6 PATIENTS BEFORE AND AFTER STARTING SUBCUTANEOUS DESFERRIOXAMINE THERAPY**

<table>
<thead>
<tr>
<th>Patient and diagnosis</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>D.F.X. therapy (mo)</th>
<th>Serum-ferritin (µg/l)</th>
<th>A.S.T. (U/l)</th>
<th>Liver-iron (µg/mg protein)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
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<tr>
<td>1 (Sid. A)</td>
<td>F</td>
<td>66</td>
<td>20</td>
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<td>600</td>
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</tr>
<tr>
<td>2 (Sid. A)</td>
<td>F</td>
<td>20</td>
<td>19</td>
<td>2240</td>
<td>1150</td>
<td>.</td>
</tr>
<tr>
<td>3 (Thal.)</td>
<td>M</td>
<td>18</td>
<td>16</td>
<td>7100</td>
<td>2500</td>
<td>33</td>
</tr>
<tr>
<td>4 (Thal.)</td>
<td>F</td>
<td>22</td>
<td>18</td>
<td>10500</td>
<td>2500</td>
<td>33</td>
</tr>
<tr>
<td>5 (Thal.)</td>
<td>F</td>
<td>12</td>
<td>12</td>
<td>16700</td>
<td>9000</td>
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<tr>
<td>6 (Thal.)</td>
<td>M</td>
<td>25</td>
<td>10</td>
<td>9450</td>
<td>2780</td>
<td>58</td>
</tr>
</tbody>
</table>

A.S.T. = aspartate transaminase.  
D.F.X. = desferrioxamine.  
Sid. A = sideroblastic anaemia.  
Thal. = beta-thalassaemia major.
results of repeat serum-ferritin estimations and liver-function tests after 5–20 months of subcutaneous d.f.x. therapy are now reported.

Results

During the first 3 months of therapy, fluctuations in serum-ferritin values obscured any definite trend. In all 34 patients, however, the serum-ferritin had fallen below the initial value 5 months after starting regular d.f.x. subcutaneously and has continued to fall (fig. 1). The steepest falls tended to occur in the patients with the highest initial levels. There was no difference in fall whether or not splenectomy had been performed. In none of the patients has the serum-ferritin concentration fallen into the normal range (14–350 μg/l), the lowest value achieved being 600 μg/l, in one of the patients with sideroblastic anaemia. 2 patients have died of congestive heart-failure during the study. These were among the patients with the highest initial serum-ferritin values (fig. 1). In 1 of these patients the serum-ferritin fell from 24,000 to 14,800 μg/l over the first 5 months of therapy but rose again to 23,000 μg/l over the following 3 months when the patient entered terminal heart-failure. The fall in serum-ferritin with d.f.x. therapy contrasts with the rising serum-ferritin values in patients studies before subcutaneous desferrioxamine therapy was started (fig. 2).

As serum-ferritin levels fell, liver function improved. Serum-aspartate-aminotransferase concentrations fell in all 17 patients tested (fig. 3). Liver-iron concentration also fell in 5 of 6 patients tested (see table).

Discussion

These preliminary results show that long-term subcutaneous desferrioxamine infusions lower body-iron stores in patients with transfusional iron overload who still need regular transfusions. Moreover, they show that iron stores, assessed by serum-ferritin, may be brought down to near normal in such patients and suggest that, with continued therapy, stores may be maintained at normal levels. This contrasts with the results with regular intramuscular d.f.x., which stabilises iron stores in patients continuing to need regular blood-transfusion, but at greatly raised and probably damaging levels.7,8

As yet, we have no definite evidence that there is improvement in heart or endocrine function in these patients. However, liver function has improved in all 17 patients followed and liver-iron concentration has fallen in 5 of 6 patients tested after more than 6 months of therapy. Thus, there is preliminary evidence that removal of iron is improving organ function in these patients in the same way as removal of iron by venesection in primary haemochromatosis. No toxic side-effects of the therapy have been noted in these 34 patients, nor in a further 23 patients whom we have treated with regular subcutaneous d.f.x. infusions for periods of 1–18 months. 1 patient had mild skin hypersensitivity to d.f.x. which was easily controlled with an antihistamine just before the nightly infusion. Local irritation at the infusion site has been mild and has not led to discontinuation of the therapy in any patient. Although 4 of our patients have died during therapy, 2 of whom are included in this report (fig. 1), they were among the oldest and most iron-loaded patients and we have no evidence that either d.f.x. or vitamin-C therapy could be implicated.

Thus, these early results suggest that long-term subcutaneous desferrioxamine infusion, given 6 nights a week over a 12 h period at a dose of 2–4 g, leads to a considerable reduction of body-iron and may lead to stabilisation of iron stores at a normal or near-normal level despite the continued need for transfusion. This is consistent with the observations that substantial iron excretion can be obtained from young patients who have had relatively few units transfused.9 Despite the high cost and inconvenience, long-term subcutaneous desferrioxamine therapy may offer the best hope of prolonging survival in a patient with a chronic refractory anaemia who requires regular blood-transfusion.

This work was supported by grants from the Wellcome Trust and from His Excellency, Mohamed Mahdi Al-Fair, United Arab Emirates Ambassador to the United Kingdom.

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REFERENCES


CYTOCHROME b IS PRESENT IN NEUTROPHILS FROM PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE

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Summary Analysis of dithionite difference spectra demonstrated that cytochrome b was present in neutrophil homogenates from a 17-year-old girl and her 25-year-old brother who had the autosomal recessive form of chronic granulomatous disease, and
from an 18-year-old boy with the X-linked form of chronic granulomatous disease. These results indicate that the postulated importance of cytochrome b in the oxygen burst during phagocytosis is questionable.

**Introduction**

CHRONIC granulomatous disease (C.G.D.) is a genetically transmitted disorder in which the oxygen-dependent antimicrobial mechanism is affected. The mode of inheritance is both X-linked (affecting mainly boys) and autosomal recessive (affecting both sexes). The defect which underlies this disorder has not been established. Deficiencies of nicotinamide adenine dinucleotide (N.A.D.H.) and nicotinamide adenine dinucleotide phosphate (N.A.D.PH) oxidase have both been postulated.

Segal and others presented evidence that a hitherto unrecognized cytochrome b is associated with the membrane of neutrophils and becomes incorporated into the vacuoles during phagocytosis. Furthermore they demonstrated that the spectrum for cytochrome b was absent in all their C.G.D. patients. They deduced that cytochrome b is part of an electron-transporting system functioning as an oxidase, which is associated with the oxygen-dependent bactericidal mechanism of the neutrophil.

The occurrence of C.G.D. in a brother and a sister has been described in association with a chemotactic defect. We decided therefore to investigate closely the neutrophils of a pair of siblings with C.G.D. Since the results of the spectral analysis contradicted those of Segal and others, we also investigated the spectrum of an unrelated patient with X-linked C.G.D.

**Methods and Results**

The methods when not specified are given in the reference to each test. Asterisks indicate that modifications have been adopted, and details of these are available upon request.

Functional tests were carried out on the leucocytes of the siblings (D, E; fig. 1) and their mother (B; fig. 1). Functional tests were normal in the mother whereas the results from the siblings were characteristic of C.G.D. Results indicated C.G.D. in patient X (fig. 2) and a carrier state of C.G.D. in his mother. The following tests were done: nitroblue tetrazolium (N.B.T.) reduction, killing of staphylococci, oxygen consumption at rest and during stimulation with serum-treated zymosan particles, liberation of $^{14}CO_2$ from glucose-$^1$C, at rest and during phagocytosis, and chemiluminescence during phagocytosis. The following functional tests were normal in all patients and their mothers: casein-induced chemotaxis and phagocytosis of paraffin emulsions before and after opsonisation with autologous serum.

The following enzymes were tested and found to be normal in all patients and their mothers: glucose-6-phosphate dehydrogenase (E.C. 1.1.1.49), 6-phosphogluconate dehydrogenase (E.C. 1.1.1.44), glutathione reductase (E.C. 1.6.4.2), and glutathione peroxidase (E.C. 1.1.1.9).

For cytochrome-b determinations 1 dl of blood was withdrawn, allowed to sediment for 30 min at $37^\circ$C in the presence of dextran and heparin. Red blood-cells were discarded and the supernatant centrifuged over 'Lymphoprep' for 15 min at 900 g (2000 r.p.m. in a MSE Mistral 4L centrifuge). Contaminating erythrocytes in the pellet were lysed twice with 20 ml of distilled water for 45 s. The neutrophils were then washed in a...
solution containing 340 mmol/l sucrose, 1 mmol/l ethylendiaminetetra-acid, pH 7.4, and 5 l.u./ml heparin. The cells were adjusted to a concentration of approximately 2.0 × 10⁷ cells ml⁻¹ (equivalent to 2 mg protein ml⁻¹) and sonicated. The dithionite difference spectra of the homogenates were determined on a Beckman 24 spectrophotometer. Spectra of all C.G.D. patients resembled those of their normal relatives and controls. There was no evidence of the shift in the myeloperoxidase peak at 474 nm that was found by Segal and others. In A, B, C, and E a shoulder was seen at 445 nm, which apparently was not related to the disease.

Discussion

The finding in the patients D and E (fig. 1) of normal uptake of test particles with abolished intracellular killing, oxygen consumption, glucose-1-C oxidation, N.B.T. reduction, and chemiluminescence establishes that these were cases of C.G.D. The fact that the mother was normal in all tests and that a brother and a sister are affected strongly indicates that this family has the autosomal recessively inherited form of C.G.D.

There have been very few reports of C.G.D. affecting siblings of both sexes. Recently Clark and Klebanoff reported C.G.D. in a brother and a sister, but they detected a chemotactic defect in the neutrophils from these two patients. In contrast to their findings, the only dysfunction we detected in the neutrophils of our cases was in the oxygen-dependent bacterial system.

The fact that cytochrome b was present in the cases of C.G.D. studied by us (both the autosomal recessive and the X-linked form) indicates that absence of cytochrome b is not always the cause of C.G.D. Therefore measurement of cytochrome b cannot be used for diagnosis in the way that oxygen-consumption studies can. Furthermore, this finding invalidates the argument that cytochrome b is part of an oxygen-consuming electron-transport system, since this argument is based on the assumption that cytochrome b is missing when, as in C.G.D., there is no oxygen consumption during phagocytosis. Perhaps other parts of the electron-transport system postulated to be present in the membranes and vacuoles of the neutrophils may be missing in our cases, and this deficiency does not show up in the dithionite difference spectra. This should be investigated.

It now has to be established whether absence of cytochrome b is associated with an abnormality of the neutrophils other than C.G.D., and to see how firmly such an abnormality is associated with C.G.D.

We thank staff and Dr Dirk Roos, Central Laboratory of the Netherlands, Amsterdam, who measured oxygen consumption, glutathione peroxidase, and 6-phosphogluconate dehydrogenase activity. We also thank Dr Anthony W. Segal, Clinical Research Centre, Harrow, who ran the spectra of the patients E and X in his laboratory in collaboration with Dr O. T. G. Jones, Department of Biochemistry, University of Bristol. We thank Mrs Gonna Gulburg, Susanne Overly, Hanne Tamstorf, and Anne-Lise Poulsen for technical assistance.

This work was supported by the Danish Medical Research Council.

Requests for reprints should be addressed to N.B.

REFERENCES


References continued at foot of next column

NON-A NON-B HEPATITIS ASSOCIATED WITH CHRONIC LIVER DISEASE IN A HEMODIALYSIS UNIT

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Summary

To clarify the aetiology of an outbreak of HB,Ag-negative acute hepatitis in the renal unit at Fulham Hospital in 1968–70, serological tests for antibody to hepatitis-A virus (anti-H.A.V.) were done retrospectively on serum samples obtained at the time of the outbreak. 7 patients had had two previous episodes of clinical HB,Ag-negative hepatitis. Serum samples were available from 24 of the 29 infected patients, and these were paired in 12 instances. There was a slight increase in the titre of anti-H.A.V. in 1 patient, and a further 2 patients who subsequently developed chronic hepatitis showed a decrease in titre, but no changes in titre were detected in the remaining 21 cases. These findings do not provide evidence for the involvement of hepatitis-A virus in the outbreak of hepatitis and effectively exclude a role for this virus in the chronic liver disease which developed subsequently in 8 (28%) of the patients. This outbreak is therefore probably non-A.

DR BORREGAARD AND OTHERS: REFERENCES—continued

non-B hepatitis, which has not been reported previously in Great Britain in a hemodialysis unit. The results confirm that this form of hepatitis may be related to a high frequency of persistent hepatic dysfunction.

Introduction

CHRONIC liver disease following acute hepatitis B is well documented both in previously healthy individuals and in patients with renal disease, but it has not been detected after serologically confirmed infection with hepatitis-A virus (H.A.V.). Persistent hepatic lesions following two outbreaks of HB,Ag-negative hepatitis thought to be due to hepatitis A have been reported in the renal unit at Fulham Hospital. Of the 29 patients who had contracted acute hepatitis in 1968–70 were subsequently found to have persistently elevated serum levels of aminotransferase activity. Liver biopsy in 7 of these patients revealed chronic aggressive hepatitis in 3, chronic persistent hepatitis in 2, and non-specific hepatitis in association with massive iron overload in 2. Since that study, serological assays for H.A.V. infection have become available, and we have now examined serum samples collected during the outbreak for antibody to H.A.V. (anti-H.A.V.) to determine if that outbreak and the succeeding chronic liver disease were related to infection with hepatitis A virus.

Patients and methods

Two or more serum samples obtained at the time of the outbreak from 24 of the 29 patients were provided by Dr Y. Cosart, Central Public Health Laboratory, London. For each patient, two serum samples were selected. In 12 of the 24 patients (group I), the first sample was obtained before the episode of acute hepatitis and the second 3 to 11 (median 8) months after the acute illness. In 7 cases (group II) the first sample was collected during the acute illness and the second during convalescence 2 to 13 (median 4) months later. In the remaining 5 patients (group III), the exact relationship of samples taken to multiple episodes of elevations in serum-aminotransferase activities was not well defined. Anti-H.A.V. was determined by immune adherence hemagglutination on serial ten-fold dilutions of heat-inactivated serum.

Of the 24 patients tested, 5 have since died from causes other than liver disease, 4 have functioning renal transplants, and 15 have been maintained on hemodialysis. The 5 patients from whom serum samples were unavailable included 2 who had died and 3 who had received successful transplants. The 8 patients who were found to have chronic liver disease are included in the 15 cases remaining on hemodialysis.

Results

The anti-H.A.V. titres obtained are shown in the table. In group I, no change in titre was apparent between the two samples in 11 of the 12 patients. The remaining patient (no. 7) demonstrated a fall from >1000 to <10 and was subsequently found to have chronic active hepatitis (case 3 of the previous report). In group II, differences in titres of anti-H.A.V. between the two samples were detected in 2 cases. In the first (no. 17), the titre increased from <10 to 100, and in the second (no. 15), a decrease from >1000 to <10 was observed. Patient 15 was subsequently found to have chronic persistent hepatitis (case 5 of the previous report). No change in titre was found in the 5 patients who comprised group III. Further analysis of the results in the 8 patients who developed chronic liver disease showed no change in anti-H.A.V. titre in 4 of the 5 included in group I (patients 1, 4, 6, 9) or in the 2 cases in group III (patients 23 and 24). As noted above, a significant decrease was observed in the remaining 2 cases (patients 7 and 15).

7 of the 24 patients tested had also developed hepatitis during a previous outbreak at Fulham Hospital in 1966, in which 14 patients contracted HB,Ag-negative hepatitis. Of the 5 included in group I, a fall in anti-H.A.V. titre was observed in 1 (patient 7) as described above. Of the other 4 patients, 2 (nos. 2 and 10) had titres of <10 in both serum samples and 2 (nos. 3 and 9) of >1000. The remaining 2 patients, patient 18 (group II) and patient 23 (group III), showed no alteration in titre (≥1000 on both occasions).

Discussion

The possibility that the 1968–70 outbreak was due to hepatitis-B virus (H.B.V.) infection seems remote, although testing for anti-HB, was not done, radioimmunoassay for HB,Ag proved consistently negative, and the prevalence of anti-HB, was no different in patients who had contracted hepatitis from those who had not. Furthermore, in the 7 patients with chronic liver disease in whom liver biopsy was performed, no hepatocytes containing HB,Ag were observed, either by fluorescence microscopy or upon orcein staining. This contrasts strikingly with the ease with which HB,Ag was detected with these procedures in hepatic tissue from renal patients with chronic liver disease related to hepatitis-B infection. The results of retrospective testing in the present study for anti-H.A.V. in 24 of the 29 patients who contracted hepatitis in 1968–70 provide no evidence for the involvement of hepatitis-A virus. Only one

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**ANTI-H.A.V. IN PATIENTS WITH ONE OR TWO EPISODES OF CLINICAL HB,Ag-NEGATIVE HEPATITIS**

<table>
<thead>
<tr>
<th>Group no.</th>
<th>No. of episodes</th>
<th>Interval between samples (mo)</th>
<th>Anti-H.A.V. titre</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sample 1</td>
</tr>
<tr>
<td>Group I:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>10</td>
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</tr>
<tr>
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<tr>
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<td>1</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>

| Group II: |                |                               |          |          |
| 13        | 1              | 3                             | <10      | <10      |
| 14        | 1              | 8                             | <10      | <10      |
| 15*       | 1              | 4                             | >1000    | >1000    |
| 16        | 2              | 1                             | <10      | <10      |
| 17        | 1              | 13                            | 100      | 100      |
| 18        | 2              | 2                             | >1000    | >1000    |
| 19        | 1              | 7                             | >1000    | >1000    |

| Group III: |                |                               |          |          |
| 20        | 1              | 8                             | <10      | <10      |
| 21        | 1              | 2                             | <10      | <10      |
| 22        | 1              | 12                            | >1000    | >1000    |
| 23*       | 2              | 3                             | >1000    | >1000    |
| 24*       | 1              | 1                             | >1000    | >1000    |

* Persistent elevation of serum-aminotransferase activity.
instance of an increase in anti-H.A.V. titre was observed overall, and this was of minor degree, falling well below the expected levels of 10 to 100 times higher. Thus, this outbreak was unlikely to have been caused by H.A.V. infection.

7 of the 24 patients who were tested had also been infected in the first outbreak of HB Ag-negative hepatitis which affected 14 patients in the renal unit at Fulham Hospital in 1966–67. Although the anti-H.A.V. titres of samples obtained from these 7 patients 3 years later do not exclude hepatitis-A infection in the first outbreak, this possibility is considerably diminished by the finding of titres <10 in both samples from 2 of these patients. This situation may be comparable to that of intravenous drug addicts who frequently suffer more than one bout of acute hepatitis unrelated to H.A.V. or H.B.V. 12 Analysis of results obtained in the 8 patients who have subsequently developed chronic liver disease revealed no change in titre of anti-H.A.V. in 6, and in the remaining 2, antibody titres had decreased in the second sample tested. Thus, it appears unlikely that the fall in antibody titre was causally related to the development of chronic liver disease, particularly since immunoglobulin levels are generally increased in such patients. 13 Other factors which may have contributed to the minor fluctuations in anti-H.A.V. titre observed include blood-transfusions and fluctuations in humoral immunocompetence. 14

Overall these results must indicate that the development of chronic liver disease was not related to hepatitis-A infection and that this outbreak falls into the category of non-A non-B hepatitis. More and more data point to this as the cause of a substantial proportion of cases of post-transfusion hepatitis negative for HB Ag15,16 and to its role in the subsequent development of chronic liver disease. 17–20 Furthermore, 7 patients developed two episodes of clinical hepatitis which was apparently not caused by H.A.V. or H.B.V. These observations support the epidemiological evidence for the existence of more than one agent of non-A non-B hepatitis. Further verification of the nature of the virus involved in this outbreak will require suitable serological tests for non-A non-B hepatitis, and experiments in which the chimpanzee was used as a model for non-A non-B hepatitis 21–23 indicate that the development of such assays may soon be realised.

We thank Mrs Doris Wong, Mrs Hazel Smith, Mrs Anthea Thornton, and Miss Carolyne Stanley for technical assistance. This work was supported in part by U.S.P.H.S. grant FO5 TW02309-02 and by grants from the Medical Research Council, the Department of Health and Social Security, and the World Health Organisation.

Requests for reprints should be addressed to R. W.

REFERENCES


REFERENCES continued at foot of next column

DEPENDENCE ON CHLORMETHAZOLOLE AND EFFECTS OF ITS WITHDRAWAL

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Summary Five cases of physical dependence on chlormethiazole are reported. Because sudden withdrawal may precipitate an acute "organic psychosis", chlormethiazole should only be used in hospitals and, even then, only for a maximum of 9 days.

Introduction

CHLORMETHAZOLE ('Heminevrin', 'Hemineurin') was introduced in 1957 and is now widely used in the treatment of delirium tremens and eclampsia. It is also used in the treatment of narcotic withdrawal. 1 Chlormethiazole is chemically related to the thiazole portion of the thiamine (vitamin B1) molecule, and it acts as a central-nervous-system depressant. The manufacturers recommend its use for "psychomotor agitation, tension and anxiety; daytime sedation in senile psychosis; confusional states; delirium tremens; sleep disturbances; withdrawal symptoms in alcoholism". In the Data Sheet Compendium 2 the statement appears "It is seldom recommended in alcoholic withdrawal to administer Heminevrin for more than nine days."

Chlormethiazole is being used frequently in general practice as an alternative to tranquillisers such as diazepam ('Valium'). We wish to draw attention to the serious addictive properties of chlormethiazole and to the considerable problems associated with its withdrawal. In our opinion it should not be recommended or used as a routine sedative or hypnotic. Its chemical relation to vitamin B1 may have created the erroneous impression that it is quite safe, harmless, and non-addictive.

Reilly 4 noted several references to abuse of chlormethiazole but found only one reported case of physiological dependence. 5 A 31-year-old man developed grand-mal status with confusional delirium, motor restlessness, and visual and auditory hallucinations. This was followed by an "organic psychosis syndrome", with paranoid features and auditory hallucinations with episodic periods

DR GALBRAITH AND OTHERS' REFERENCES—continued

of chiefly confusional behaviour or hallucinatory activity, which lasted for 8 days. Reilly reported a second case of physiological dependence with an organic psychosis after withdrawal of chlorpromazine.

Case-reports

Five cases of physical dependence on chlorpromazine are reported. In four of these cases withdrawal was associated with signs of an organic psychosis.

Case A

A 47-year-old housewife was prescribed 2-5 g chlorpromazine daily by her general practitioner because of alcohol abuse. However, she took up to 5 g daily. This practice continued for 3 years until she was referred to a psychiatric outpatient clinic where she was seen by one of us (M. H.). Chlorpromazine was discontinued, but the same night she became excited with uncontrolled tremulousness, crying, suicidal tendencies, visual and auditory hallucinations, ideas of reference, derealisation, depersonalisation, and disorientation to time, place and person. She was admitted as an emergency, and haloperidol was used for further withdrawal. The acute phase resolved within 3 days. However, 4 weeks later there was still pronounced disturbance of sense of time, memory impairment, derealisation, and depersonalisation. She has since recovered fully, though she continues to receive help with her personality difficulties and affective disturbance.

Case B

A 72-year-old man was admitted after an overdose of nitrazepam. He had been taking chlorpromazine for 2 years as a night sedative. All medication was stopped and at 3 A.M. on the morning after his admission he became disorientated, confused, and noisy. He was disoriented in time and place, apparently hallucinating, and had inability of affect. He was given chlorpromazine 500 mg three times a day and 1-5 g at night and rapidly recovered; 24 hours later he was free from hallucinations or delusions. Subsequent gradual withdrawal was associated with a period of anxiety, agitation, paranoid delusions, and visual and auditory hallucinations lasting 5 days.

Case C

A 58-year-old alcoholic-dependent man admitted taking up to 10 g of chlorpromazine a day. We attempted to reduce the dose to 2 g a day but reduction was accompanied by an episode of abdominal pain, marked anxiety, and visual hallucinations, and he refused to cooperate further in a dosage-reducing programme.

Case D

A 48-year-old housewife with a phobic anxiety state had been treated for 2 years with chlorpromazine 2 g at night and 3 g during the day. When the dose was reduced she experienced agitation, anxiety, severe insomnia, and mild confusion. Withdrawal was finally achieved during a stay in hospital.

Case E

A 64-year-old anxious and depressed woman was receiving up to 4 g of chlorpromazine at night. The patient admitted to using larger amounts whenever she felt anxious. We attempted to replace chlorpromazine with flurazepam but the patient initially resisted withdrawal of the chlorpromazine. With great difficulty gradual substitution of chlorpromazine by a benzodiazepine was undertaken with the active cooperation of the patient and the general practitioner. Eventually these efforts were successful.

Discussion

Only two of our five cases had a history of drug or alcohol abuse. The remaining three could not be regarded as having addiction-prone personalities and in all five cases we believe that psychological dependence was not the most important factor in the dependency. We consider that they all had become physically dependent on chlorpromazine. It seems that after 2 g a day for 2 years, dependence is such that severe withdrawal symptoms can be expected. Many patients in the U.K. may be receiving chlorpromazine as a routine sedative or hypnotic on the mistaken belief that it is a safe, harmless, and effective drug related to vitamin B6. Patients are probably unaware of their physiological dependence and do not appreciate the risk of inadvertent withdrawal, cessation, or interruption. Suicidal depression or an acute psychotic state are likely consequences.

Chlorpromazine should only be used for inpatient treatment of acute alcoholic withdrawal symptoms, eclampsia, and narcotic withdrawal symptoms. Even in these cases we support the recommendation that it should never be given for more than 9 days. We suggest that treatment of all patients currently receiving chlorpromazine should be reviewed. In our opinion hospital admission should be considered for the withdrawal period. Information about the dangers of this drug should be sent to all doctors as a matter of urgency and the manufacturers' literature and presentations about chlorpromazine should be reconsidered.

Requests for reprints should be addressed to M. A. H.

REFERENCES
2. Monthly Index of Medical Specialities, 1979, vol. 21, no. 4, p. 87.

Preliminary Communication

THERAPEUTIC EFFICACY OF APOMORPHINE COMBINED WITH AN EXTRACEREBRAL INHIBITOR OF DOPAMINE RECEPTORS IN PARKINSON’S DISEASE

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Summary

Apomorphine in combination with a peripheral dopamine receptor blocker (domperidone) was administered to four parkinsonian patients in a double-blind placebo-controlled study. The therapeutic efficacy of apomorphine was not reduced by domperidone, while nausea, drowsiness, sedation, and arterial hypotension were prevented. Combination of domperidone with dopamine agonists may result in more effective treatment of Parkinson's disease.

INTRODUCTION

Apomorphine, a direct stimulant of dopamine (D.A.) receptors, is effective in relieving neurological symptoms...
in Parkinson’s disease but its usefulness is limited by its short-term action and by side-effects such as drowsiness, yawning, nausea and vomiting, arterial hypotension, and hormonal changes. The therapeutic effect is the result of selective stimulation of D.A. receptors present in brain structures, the caudate nucleus and nucleus accumbens, which are inside the blood-brain barrier (B.B.B.), whereas most of the side-effects seem to be due to the stimulation of D.A. receptors in brain structures outside the B.B.B. (area postrema, median eminence, pituitary) or in peripheral organs such as the stomach. Combination of apomorphine with a D.A. receptor blocker which does not cross the B.B.B. may counteract the side-effects while preserving the therapeutic properties of apomorphine.

Dopemifone [5-chloro-1(3-[2,3-dihydro-2-oxo-1H-benzimidazole-1-yl]propyl)-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one] is a D.A. receptor blocker which does not penetrate the B.B.B. It is used as an antieptic.

**PATIENTS AND METHODS**

Four patients with Parkinson’s disease with “moderate disability” according to the Webster scale who had received no medication for at least three weeks, took part in two drug trials separated by 3–4 days. In a double-blind study saline (2 ml intramuscularly) or dopemifone (100 µg/kg intramuscularly) was given 60 min before apomorphine (20 µg/kg intramuscularly). Neurological symptoms were scored according to Cotzias et al. before and after each drug administration. Every 30 min arterial pressure was measured, and side-effects were evaluated, for 2 hours.

**RESULTS**

After saline and apomorphine all the patients were drowsy and sedated, and some complained of nausea and discomfort. Although rigidity and tremors were markedly reduced (mean improvement 33-8%), patients were apathetic during evaluation. Yawning episodes and the decrease in blood-pressure were observed in some patients (see table). These effects began a few minutes after apomorphine administration and lasted for up to 40 min; they were most pronounced 15–20 min after administration. After dopemifone and apomorphine patients had none of the side-effects usually induced by apomorphine except yawning. Repeated and loud yawns (up to 15) occurred in case 2 and 4. Feelings of calmness and well-being were reported by the patients, who willingly cooperated in neurological evaluations. Almost all the adverse effects of apomorphine were prevented by dopemifone, and the improvement in parkinsonian symptoms was not only unaffacted but also further enhanced (mean improvement 43.3%). Analysis of each item in the Cotzias scale demonstrated that this further improvement was due to a reduction in akinesia, conceivably the result of less drowsiness and fewer side-effects. Saline or dopemifone alone did not induce a statistically significant change in the mean disability score.

**DISCUSSION**

Dopemifone, a peripheral D.A. receptor blocker, prevented apomorphine-induced nausea, drowsiness, sedation, and arterial hypotension. This indicated that these changes may be caused by the stimulation of extracerebral D.A. receptors. The receptors responsible for nausea and vomiting are in the area postrema which is outside the B.B.B. It is more difficult to explain the finding that apomorphine-induced drowsiness was affected by dopemifone in our parkinsonian patients, but possible involvement of D.A. receptors in peripheral organs, such as the pituitary or stomach, is worth checking. D.A. receptors in renal artery are unlikely to account for the effect of dopemifone on drowsiness, but these receptors may be involved in arterial hypotension induced by apomorphine. Indeed this effect on blood-pressure is often observed with D.A. agonists, and experiments on dogs have confirmed that apomorphine-induced hypotension is not a centrally mediated phenomena.

The only behaviour unaffected by dopemifone, and even enhanced by it, was yawning, which seems to be mediated centrally. Yawning in man is antagonised by haloperidol, and this finding confirms that dopamine has a definite role in controlling such behaviour.

Modification of therapy based on the clinical evidence presented above would make apomorphine a more useful therapeutic agent, but apomorphine treatment of Parkinson’s disease has other limitations. More suitable D.A. agonists could be used in combination with dopemifone. Bromocriptine and piribedil (ET-495), two of the best known dopamine agonists, are useful therapeutic agents in Parkinson’s disease. However, bromocriptine and piribedil induce side-effects which may limit use of these agents. These effects may also be due to D.A. receptor activation; if so a peripheral blocker could be used to eliminate them. Similar difficulties are found with levodopa therapy.

**EFFECTS OF APOMORPHINE AND DOMPERIDONE IN 4 PATIENTS WITH PARKINSON’S DISEASE**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Webster score on admission*</th>
<th>Saline + apomorphine</th>
<th>Domperidone + apomorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Side-effects</td>
<td>Neurological improvement (%)</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>59</td>
<td>15</td>
<td>Nausea, sedation,</td>
<td>27.5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>hypotension</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>17</td>
<td>Nausea, drowsiness,</td>
<td>40.3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>yawning</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>61</td>
<td>13</td>
<td>Drowsiness, pallor,</td>
<td>35.6</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>hypotension, yawning</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>15</td>
<td>Nausea, drowsiness,</td>
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<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.8</td>
</tr>
</tbody>
</table>

*see ref. 11.
D.A. agonists improve abnormal involuntary movements in Huntington's chorea,18,19 and mental state in mania20 and schizophrenia.21,22 Thus our findings may have applications in other types of treatment. Combination of D.A. agonists (apomorphine in particular) with an extracerebral inhibitor of D.A. receptors may make such agonists more useful therapeutic agents.

We thank Dr Francesco Mastini of the General Hospital of Ghi- larza (Nuoro) for skilful assistance and Janssen Pharmaceutica for the generous supply of domperidone.

Requests for reprints should be addressed to G. U. C., Institute of Pharmacology, University of Cagliari, Via Porcell 4, 09100 Cagliari, Italy.

REFERENCES


Reviews of Books

Hematology


Few textbooks on medical specialties are written primarily for undergraduates, and these tend to be didactic presentations of the essentials, trimmed of explanation and interest. In contrast, Paul Reich’s highly informative and easily read text, with its attractive format, is likely to be widely used by hematologists as the basis of, or model for, undergraduate teaching. The series of which this book is the first volume is intended to bridge the gap between the undergraduates’ basic science course and a clinical clerkship. If this first text is representative, the series may contribute as much to bridging the gap as any re-organisation of the medical curriculum. Dr Reich, with ten years’ experience of the Harvard Medical School course in haematology, covers the important aspects of the specialty from anaemia to the lymphomas in ten chapters, while Daniel Deykin writes on hemostasis. There are 72 high-quality colour photomicrographs to illustrate cell morphology, and the chapters include case-development problems to test understanding, discussion topics for seminars, and well-selected references. Although written for the undergraduate, there is so much information that the book will appeal also to graduates, including haematology trainees. One can but hope that undergraduates will have the time to absorb at least some of it.

Hematology for Practitioners


Haematological disorders often impinge on general medical practice, and vice versa. This book, written for the general physician who has to treat haematological disease on his own or in conjunction with a haematologist, will foster a good relationship between the two groups of practitioners. The 31 authors have written 22 chapters in a uniform, attractive style with the emphasis on diagnosis and investigation. The chapter headings of this book incorporate a useful problem-oriented approach to the investigation and diagnosis of haematological disorders. Since advice on treatment, which is “often orchestrated by the specialist”, is limited to principles, the book should not date rapidly. The amount of detailed information in the text is necessarily limited, but it is extremely well selected, and there is a great deal of useful clinical data. The advice given relates to day-to-day problems ranging from the dangers of a purely clinical diagnosis of leg-vein thrombosis in nurses to the psychological management of the patient with a haematological malignancy. In addition, basic principles of tumour-growth patterns in relation to chemotherapy, blood component therapy, genetic counselling, Giemsa-banding of chromosomes, and the investigation of bleeding disorders or hypergamaglobulinaemia are explained concisely. Haematologists, both experienced and in training, will also find much useful information in this well-balanced text.

Current Topics in Hematology


The editors describe the advance of hematology as resembling an ameboid motion—some parts seem static while others are “propelling forward in a continuous exchange of apparent rest and rapid explosive extrusions”. Current Topics in Hematology is a new series which aims to reflect this motion. There will be no themes or rigid publishing deadlines, but new volumes will appear as knowledge unfolds. If this means that paper will not be wasted on descriptions of worn-out paths so much the better, but researchers may well find that only one chapter in any volume will interest them. Three of the five chapters in this volume are on red-cell metabolism and function. The chapter on human erythrocyte glucose-6-phosphate dehydrogenase, by L. Lazzatto and U. Testa, is a generally well-explained account of enzyme structure and function in normal and mutant subjects; it incorporates unpublished information, but is slightly marred by several printing errors. N. Mohandas and S. B. Shohet give a good description of control of red-cell deformability and shape, and

The Lancet, May 5, 1979

ADDENDUM

Since this paper was written, Y. Agid and others (Lancet, 1979, i, 570) have reported the usefulness of domperidone in preventing some side-effects of bromocriptine and in improving its efficacy in Parkinson’s disease.