oral contraceptives makes this unlikely. An alternative explanation is that the hormonal changes induced by pregnancy and oral contraceptives cause an increase in membrane permeability to sodium and stimulate sodium efflux. If this were the case then there must be an agent present in normal pregnancy which stabilises the cell membrane and which is absent or diminished in hypertensive pregnancy.

It has been suggested that prostacyclin mediates the tolerance to angiotensin II in normal pregnancy and that its relative lack is responsible for the onset of hypertension.⁷ This hypothesis is compatible with our results, since it has also been found that oral contraceptives inhibit prostacyclin production,⁸ and that long term use of oral contraceptives is associated with a significant and reversible rise in blood pressure.⁹ Our results offer an explanation for this phenomenon, since the increased cell membrane permeability to sodium occurring in women taking oral contraceptives was similar to that occurring in hypertensive pregnancy. Indeed it has been suggested that women most likely to have a rise in blood pressure while taking the pill are those who have had pre-eclampsia.^{10 11}

In order properly to evaluate the hormonal influences of pregnancy and oral contraceptives on cellular sodium handling longitudinal studies are required so that changes within subjects can be monitored.

This study was partly supported by a grant from the Central Birmingham Health District Endowment Research Committee.

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(Accepted 1 June 1983)

Intermittent cyclophosphamide in refractory rheumatoid arthritis

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Abstract

Three patients with refractory rheumatoid arthritis were treated with oral cyclophosphamide; in two cases this was supplemented with pulse treatment with methylprednisolone. Long term remission was induced in all three patients and was sustained until follow up at least nine months after the methylprednisolone was stopped. Leucopenia occurred but resolved when cyclophosphamide was reduced from daily to intermittent dosing.

Intermittent treatment with cyclophosphamide, possibly in conjunction with pulses of methylprednisolone, may induce remission in patients with rheumatoid arthritis refractory to other forms of treatment.

Introduction

Recently the possibility of managing refractory rheumatoid arthritis has increased with the availability of various immuno-

suppressive regimens, among them cytostatic treatment and intravenous methylprednisolone pulse treatment. Use of a combination of corticosteroids and intermittent cytostatic treatment, which is well established in treating cancer,¹ has not been described in rheumatoid arthritis resistant to treatment, although Fosdick *et al* reported using intermittent cyclophosphamide treatment in a few patients with rheumatoid arthritis.²

We report the effect of combined intermittent cyclophosphamide treatment and methylprednisolone in three patients with disabling rheumatoid arthritis that had been impossible to control adequately either because of toxic side effects or because of failure to respond to treatment.

Case reports

Case 1—A 60 year old woman with seropositive erosive rheumatoid arthritis of four years' duration had been treated with low dose prednisone, gold, and penicillamine. In July 1981, as disease activity persisted (table), oral cyclophosphamide was started at a dose of 100 mg/day, which was reduced to 50 mg/day when leucopenia ($2.9 \times 10^9/l$) occurred. As the leucopenia continued intermittent treatment with cyclophosphamide 100 mg every three and subsequently every four days was begun, which completely abolished the symptoms. In May 1983 the disease was still in remission (table).

Case 2—A 51 year old woman with seropositive erosive rheumatoid arthritis of six years' duration had received treatment with gold, chloroquine, penicillamine, and azathioprine. As her disease remained active (table), in September 1981 she was placed on a regimen of methylprednisolone pulse treatment 1 g intravenously on four successive days and oral cyclophosphamide 100 mg/day. As the disease activity did not abate, repeated courses of methylprednisolone pulse

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Clinical details of three patients before and after cyclophosphamide treatment

	Case 1		Case 2		Case 3	
	Before	After (May 1983)	Before	After (May 1983)	Before	After (May 1983)
Morning stiffness (hours)	1	< 1	3	< 1	1	< 1
Erythrocyte sedimentation rate (mm in first h) (Westergren)	77	46	100	20	120	30
Haptoglobulin (g/l) (normal 0.3-2.8 g/l)	5.2	1.2	6.0	2.7	9.9	1.2
Rose-Waaler titre	5120	320	2560	160	160	40
Haemoglobin (g/dl) (normal 11.3-15.0 g/dl)	11.4	13.0	11.3	12.1	10.9	11.6
Leucocytes ($\times 10^9/l$)	5.2	6.1	9.2	6.5	9.0	4.0
Previous treatment	March 1979—Oral prednisone 30 mg/day, tapered over 2 weeks; transitory effect. Feb-Aug 1980—Aurothiomaleate 1110 mg intramuscularly; no response. Oct 1980-July 1981—Penicillamine, maximum 625 mg/day; no response.		March 1978—Aurothiosulphate, total of 150 mg intravenously; stopped owing to haematuria. April 1978-July 1980—Chloroquine 250 mg/day six days a week; response followed by relapse. July 1980-April 1981—Azathioprine 100 mg a day; no response. April-Sept 1981—Penicillamine, maximum 500 mg/day; withdrawn because of erythema multiformis bullosa.		1960—Aurothiosulphate, total of 560 mg intravenously; no response. 1975—Chloroquine 250 mg six days a week; no response. March 1976-April 1977—Aurothiosulphate, total of 1900 mg intravenously; no response. Sept 1978-Oct 1980—Chloroquine 250 mg/day six days a week; response followed by relapse. Oct 1980-Nov 1981—Penicillamine maximum 625 mg/day; no response. Nov 1981-Feb 1982—Azathioprine 100 mg/day; no response. Feb-May 1982—Levamisole 150 mg/week; no response.	
Methylprednisolone pulse treatment			22-25 Sept 1981—1 g/day intravenously. 1-4 Dec 1981—1 g/day intravenously. 15-18 Feb 1982—1 g/day intravenously. 10-13 May 1982—1 g/day intravenously. 16-19 Aug 1982—1 g/day intravenously.		11-14 May 1982—1 g/day intravenously. 29 June-2 July 1982—1 g/day intravenously.	
Cyclophosphamide treatment	From 27 April 1981, 100 mg/day.		From 20 Oct 1981, 100 mg/day.		From 11 May 1982, 100 mg/day.	
	From 4 Feb 1983, 100 mg every four days.		From 21 Dec 1982, 100 mg every four days.		From 13 Oct 1982, 200 mg every four days.	

treatment were given until August 1982, when leucopenia ($2.7 \times 10^9/l$) occurred. Treatment was changed to intermittent cyclophosphamide 100 mg every three and later every four days, which abolished the symptoms. In May 1983 the disease was still in remission (table).

Case 3—A 51 year old woman with a 25 year history of seropositive erosive rheumatoid arthritis had been treated with gold, chloroquine, low dose prednisone, penicillamine, azathioprine, and levamisole. In May 1982 because of persisting disease activity (table) she was given methylprednisolone pulse treatment 1 g intravenously on four successive days and oral cyclophosphamide 100 mg daily increasing to 150 and 100 mg on alternate days. Methylprednisolone pulse treatment was repeated in June 1982. Leucopenia ($3.0 \times 10^9/l$) occurred, and in September 1982 intermittent cyclophosphamide treatment was begun with 100 mg every two and later every four days; this completely suppressed the disease. In May 1983 the disease was still in remission (table).

Discussion

Immunosuppressive agents are increasingly used to manage rheumatoid arthritis, the purpose being to suppress the abnormal immune mechanisms that are supposed to play an essential part in the pathogenesis of the disease. Disease activity may be controlled by cyclophosphamide,^{2,3} but continuous treatment is often complicated by leucopenia; the degree of leucopenia is directly proportional to the dosage of cyclophosphamide.⁴ Fosdick *et al* used intermittent cyclophosphamide treatment in patients with rheumatoid arthritis in whom the leucocyte count tended to drop.²

Between June 1981 and June 1983 we gave intermittent cyclophosphamide treatment to three patients with refractory seropositive erosive rheumatoid arthritis; in two this treatment was supplemented initially by courses of methylprednisolone pulse treatment, but in both cases methylprednisolone was stopped at least nine months before the follow up examination in May 1983. This regimen induced long term remission in all

three patients. Toxic reactions were avoided and leucopenia curbed, and intercurrent infections requiring treatment did not occur.

Hazleman found an increased incidence of infection during immunosuppressive treatment, particularly when it was combined with massive doses of corticosteroids.⁵ Our patients had no infections. The explanation might be that the intermittent cytostatic treatment given was less immunosuppressive, or that glucocorticosteroids given as methylprednisolone pulse treatment are less immunosuppressive than continuous oral glucocorticosteroids. Bladder fibrosis is another side effect that seems to be related to the dosage of cyclophosphamide. None of our patients had symptoms of the urinary tract.

In conclusion, we consider that intermittent cyclophosphamide treatment, possibly combined with courses of methylprednisolone pulse treatment, may produce long term remission in patients with resistant forms of rheumatoid arthritis, having a lower tendency to induce leucopenia and, possibly, a reduced risk of late adverse reactions.

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(Accepted 17 June 1983)