Polymyalgia rheumatica

Abrupt and gradual withdrawal of prednisolone treatment, clinical and laboratory observations

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SUMMARY Eighteen patients with polymyalgia rheumatica had corticosteroid treatment withdrawn abruptly under close observation. In each case polymyalgic symptoms reappeared but were controlled rapidly when prednisolone was reintroduced. Prednisolone withdrawal was then started by slow decrements of dose. In no patient was it possible to withdraw prednisolone treatment, after using either method, during the period of observation.

Polymyalgia rheumatica (PMR) is a condition probably half as frequent as rheumatoid arthritis in patients over 70 years (Dixon *et al.*, 1966). The symptoms respond rapidly to corticosteroids which, unlike nonsteroidal anti-inflammatory agents, prevent possible major vascular complications (Easterbrook *et al.*, 1967; Wadman and Werner, 1967). Although the disease can be self-limiting, as shown by the reports on its natural history (Gordon, 1960; Bagratuni, 1963), corticosteroid therapy has not eliminated instances of disease which require treatment for 5 years or more, as shown by Myles (1975) and by several patients in the present study. Prolonged corticosteroid treatment is not without hazards in the elderly and we have therefore studied the effects of withdrawing it, both abruptly and gradually in the same patients. Corticosteroids have been safely withdrawn abruptly in other diseases provided the patients were closely observed (Robinson *et al.*, 1962; Livanou *et al.*, 1967).

Patients

The criteria for the diagnosis of PMR were previously described (Dixon, 1969). 18 outpatients (7 men, 11 women) taking corticosteroid treatment for PMR in stable dosage, were studied and details are given in Table 1. None had presented with any of the clinical signs which are known to correlate with histologically proven temporal arteritis (Dixon *et al.*, 1966). Their ages ranged from 47 to 91 years, mean 69 years. The duration of corticosteroid treatment before the study varied from 9 to 96 months, mean 27 months. One

patient (Case 18) had had a remission period of 16 months without corticosteroids but subsequently relapsed and required further treatment. She entered the study in the eighth month of her relapse.

Methods

Each patient was transferred, if necessary, from the maintenance dose of corticosteroids to the nearest equivalent dose of prednisolone in plain white scored tablet form. This is set out in Table 2 (period A). The dose of prednisolone thus achieved varied from 2.5 to 15 mg, with a mean of 8.5 mg/day. The patients were observed and confirmed to be symptom free on this dose (period B) for at least one week before prednisolone withdrawal. The latter (period C, Table 2) was achieved by substitution of white tablets of ascorbic acid of identical appearance. Patients were told simply that they should try the new tablet for a week and report back at the next interview. They were allowed to revert to the prednisolone tablets if they became very uncomfortable. If no relapse had occurred after one week a further week of placebo treatment followed.

Period D, when prednisolone was reintroduced, was continued until a stable dosage had been achieved. Period E, the period of slow, step-wise reduction of prednisolone, lasted for up to 6 months. The patients were followed weekly during periods A, B, C, and D, and monthly during period E. Before study and at the beginning and end of each period observations were made on the erythrocyte sedimentation rate (ESR) measured by the Westergren method, plasma viscosity measured in the Harkness viscometer, serum iron, serum iron binding

Table 1 Clinical and biological features of 18 patients with PMR, at the beginning and end of study

Case no.	Age (years)	Sex	Duration previous treatment (m)	Initial (period B, Table 2)			Follow-up duration (m) (periods D and E, Table 2)	Final (end of period)			Additional pathology or medication
				Plasma viscosity (cp)	ESR (mm/h)	Prednisolone dose (mg/d)		Prednisolone dose (mg/d)	Plasma viscosity (cp)	ESR (mm/h)	
Group 1											
1	70	M	24	1.63	4	2.5	3	1.0	1.65	2	—
2	76	M	48	1.63	5	10.0	5	5.0	1.75	4	—
3	59	M	9	1.63	5	10.0	2	6.0	1.60	7	Urethritis
4	68	M	12	1.65	10	10.0	5	6.0	1.62	17	Sciatica
5	66	F	16	1.62	11	10.0	5	4.0	1.59	10	Hypertension
6	60	F	16	1.26	15	10.0	6	7.5	1.68	24	—
Group 2											
7	76	F	24	1.73	21	10.0	5	8.0	1.64	24	Chondrocalcinosis of knees
8	47	F	12	1.70	22	2.5	6	4.0	1.65	14	—
9	84	M	96	1.59	26	10.0	1	10.0	1.62	55	Osteoarthritis of hip treated with indomethacin; died of bleeding duodenal ulcer
10	68	F	42	1.66	32	7.5	4	7.5	1.70	30	—
Group 3											
11	67	M	12	1.80	20	15.0	4	10.0	1.88	10	—
12	74	M	24	1.74	24	7.5	5	7.5	1.67	11	Hypertension treated with methyl dopa
13	69	F	24	2.02	29	10.0	6	8.0	1.82	16	—
14	66	F	24	1.81	30	10.0	5	4.0	1.85	26	Osteoarthritis of knee
15	51	F	18	1.75	33	5.0	2	4.0	1.79	15	—
Group 4											
16	91	F	42	1.98	55	7.6	6	5.0	1.85	87	Cardiac failure
17	74	F	16	1.89	63	5.0	3	5.0	1.94	69	—
18	69	F	12+8	2.01	98	10.0	1	10.0	1.90	53	Died of carcinoma of ovary

cp = centipoise

Table 2 General plan of prednisolone withdrawal

Period A	Changeover from prestudy corticosteroid to nearest convenient equivalent dose of prednisolone
Period B	Stabilization before stopping prednisolone
Period C	Abrupt withdrawal of prednisolone by substitution of placebo, terminated by recurrence of symptoms < 1 week in 3 patients 1 week in 12 patients 2 weeks in 2 patients 10 weeks in 1 patient
Period D	Restabilization on prednisolone at prewithdrawal dosage
Period E	Gradual prednisolone withdrawal

capacity, white cell count (WBC), haemoglobin, and serum alkaline phosphatase in King-Armstrong units (KAU). Each patient was given a personal assessment chart (visual analogue scale) to monitor daily progress with regard to pain, stiffness, and general well-being, and a detailed questionnaire concerning the initial picture of the disease. This, together with the available clinical record, enabled us to correlate features of any relapse with the original presenting syndrome.

Results

CLINICAL RESPONSE TO RAPID PREDNISOLONE WITHDRAWAL (PERIOD C, TABLE 2)

All patients had a recurrence of their polymyalgic symptoms. The symptoms of the relapse always

included those with which the patient originally had presented. Thus, when the original symptoms were in the upper limb girdle the recurrence always affected the same area, although in some patients additional clinical features induced by the relapse were observed, namely synovitis of the knee (Case 11) and of the sternoclavicular joint (Case 15). No patient developed symptoms or signs of cranial arteritis.

Polymyalgic symptoms recurred within one week of withdrawal of prednisolone in 15 patients. In 3 of them (Cases 6, 11, 14) the relapse was severe and rapid enough to make them revert to their original dosage within 4 days. 2 patients (Cases 2, 15) remained symptom free for 2 weeks before relapsing and one (Case 1) remained asymptomatic for 10 weeks. He then relapsed but obtained relief of symptoms from 10 mg prednisolone twice weekly, on which dose his ESR and plasma viscosity were normal.

LABORATORY FEATURES OF RAPID PREDNISOLONE WITHDRAWAL (PERIOD C, TABLE 2)

ESR and plasma viscosity (Fig. 1)

Two patients (Cases 1, 14) could not be reassessed early enough to detect a possible rise in ESR in relation to their clinical relapse. 3 patients who remained well for one week (Cases 3, 5) or 2 weeks

(Case 2) before having a relapse requiring the drug to be reintroduced showed no rise of ESR above 30 mm/h, nor did plasma viscosity measured at the time rise above the upper normal limit, and therefore did not seem to provide an earlier or more sensitive index.

Fig. 1 Individual changes in ESR in 16 patients (case numbers are given).

For patients who reverted to the original dose of prednisolone before the planned review at one week it was not possible to determine the exact time of relapse of the indices of disease activity. However, 2 of them (Cases 6, 11) were reassessed not more than 4 days after reintroduction of prednisolone when their ESRs were still raised and for assessment purposes they have been grouped with the 11 remaining patients who completed one week (Cases 4, 7–10, 12, 13, 16–18) or 2 weeks (Case 15) of prednisolone withdrawal. These 13 patients showed a mean rise of ESR from 35 to 65 mm/h.

Other laboratory measurements

Table 3 gives the mean values of Hb, WBC, serum iron, and serum iron binding capacity before, during, and after completion of prednisolone withdrawal in

the 16 patients for whom appropriate data were available. Values for serum alkaline phosphatase were normal and remarkably constant, apart from one patient (Case 6) who showed a slight rise when prednisolone was withdrawn (Fig. 2).

Table 3 Mean changes in four indices in 16 patients in whom maintenance prednisolone dose was abruptly withdrawn and reintroduced later

	Period B (Table 2) Maintenance dose of prednisolone prewithdrawal	Period C Placebo for at least one week	Period D Prednisolone reintroduced
Hb (g/dl)	13.6	13.2	13.1
WBC (/mm ³)	8200	7500	8300
Serum iron (µg/100 ml)	71	63	74
Total iron-binding capacity (µg/100 ml)	300	305	302

Changes not statistically significant.

Conversion: Traditional units to SI—White blood count: 1000/mm³ ≈ 1.0 × 10⁹/l. Serum iron and total iron binding capacity: 1 µg/100 ml ≈ 0.179 µmol/l.

Fig. 2 Alkaline phosphatase levels in 12 patients in whom serial measurements were obtained. Before (period B) and after (period C) prednisolone withdrawal, and after reintroduction of prednisolone (period D).

REVIEW AFTER REINTRODUCTION OF PREDNISOLONE (PERIOD D, TABLE 2)

On reintroduction of prednisolone 14 patients became asymptomatic in less than one week. Cases 2 and 15 required 2 weeks (these 2 patients also took 2 weeks for symptoms to recur after prednisolone withdrawal). Case 11 remained mildly symptomatic until 2 months after reintroduction of prednisolone treatment. Case 10 had to have her dose temporarily increased to control symptoms and a raised ESR.

Frequent ESR measurements to detect accurately

the time of return to prewithdrawal level after prednisolone was reintroduced were feasible in only 9 patients and delay ranged from 1 week to 2 months.

PERIOD OF GRADUAL WITHDRAWAL OF PREDNISOLONE (PERIOD E, TABLE 2)

We divided the patients into four groups before prednisolone withdrawal.

- (i) 6 with both normal ESR and PV (plasma viscosity) ($\text{ESR} \leq 15 \text{ mm/h}$, $\text{PV} \leq 1.72 \text{ cp}$).
- (ii) 4 with a normal PV but a moderately raised ESR. In the past we have arbitrarily accepted 30 mm in one hour as the upper limit of safety in elderly patients with PMR controlled by corticosteroid treatment (Dixon, 1970).
- (iii) 5 who had a moderately raised ESR and a raised PV.
- (iv) 3 with a raised PV and a rapid ESR.

Once satisfactory symptomatic control had been re-established a stepwise reduction of prednisolone was attempted (Table 1). In all patients in group 1 progressive withdrawal was possible at a mean rate of 1 mg per month over a 4- to 5-month period. In group 2 it was possible to reduce the dose in only one patient, while Case 8 required a temporarily increased dose. Case 9, who was also taking indomethacin for osteoarthritis of the hip, died suddenly due to profuse bleeding from an asymptomatic and previously unsuspected duodenal ulcer. His ESR remained high until death. In group 3 the rate of dose reduction possible was only an average of 0.5 mg per month over a mean 4-month period. In spite of this, 4 out of these 5 patients had persistently high PVs even though the ESR remained normal. In group 4 Case 18 showed a substantial reduction in ESR one month after being treated with prednisolone in the prewithdrawal dosage. She was free of symptoms from PMR but later developed an abdominal mass and died of carcinoma of the ovary after one month. The other 2 patients in this group also continued to be symptom free, despite a markedly raised ESR, and were given a short trial of large doses of prednisolone which had no further effect on the ESR. In view of the lack of symptoms, the initial dose was resumed without ill effects.

Discussion

Relapse of PMR occurred in all patients when corticosteroid treatment was stopped abruptly or gradually reduced. At no time were clinical signs of adrenal insufficiency detected and the symptoms were always specific enough to exclude those noted by normal people on steroid withdrawal (Good *et al.*, 1959) or the steroid 'pseudorheumatism' syndrome (Hargreave *et al.*, 1969). The symptoms in all

patients reproduced the original complaints at the time of diagnosis and in 2 were accompanied by a return of previously documented physical signs. Also, on abrupt withdrawal of prednisolone a rise of the ESR above 30 mm/h was observed in 13 of our 18 patients. The mean rise was 35 mm/h and the mean peak achieved was 65 mm/h. This confirms Paulsen and Iversen's (1971) observation that of 1 patients in whom a clinical relapse of PMR occurred on attempting to reduce or stop corticosteroid treatment, 8 developed an ESR above 25 mm in one hour.

Two of our patients (Cases 1, 14) could not be reassessed early enough to detect a possible rise in ESR in relation to their clinical relapse. The remaining patients (Cases 2, 3, 5) showed only a slight rise in ESR, not reaching 20 mm in one hour in spite of having a definite clinical relapse of PMR. They may be compared with those reported by Paulley and Hughes (1960), Bruk (1967), and by Mowat and Hazelman (1974) with a normal or low presenting ESR. The PV of these 3 patients also remained in the normal range. This suggests that the PV is not more sensitive than the ESR in this situation. When comparing patients of groups II and III it appeared that 2 out of the 3 subjects who went back on prednisolone treatment in less than a week, possibly owing to a more active underlying disease, belonged to group III, i.e. had an initial ESR at the same level as the patients of group II but had a moderately raised PV in addition. The clinical significance of the latter may therefore be greater in ranges of inflammatory activity where ESR is already slightly raised. A more detailed account of the relationship between the ESR and PV in PMR and rheumatoid arthritis is given elsewhere (Esselinckx *et al.*, 1977).

The initial ESRs (Table 1) did not correlate with the duration of previous disease and treatment, nor with the current dose of prednisolone, reflecting the wide individual variation in the course of PMR, as reported by others. Myles (1975) found that corticosteroid treatment could be stopped after 3 months to 3½ years in 14 patients, but 14 other patients still required corticosteroid treatment after more than 5 years. These figures for the duration of the disease are in fact similar to those of the precorticosteroid era, when Gordon (1960) observed a natural history of 2 to 4 years in 7 patients, and Bagratuni (1963) a mean overall duration of symptoms of 7.1 years in 50 patients, in some of whom symptoms were present for 14 years. However, the initial ESR levels seem to allow some prediction of the outcome upon withdrawal of corticosteroids and consequently as to the occult disease activity in patients kept asymptomatic on a maintenance dose.

Thus, group I included the patients whose ESR

did not rise significantly upon abrupt corticosteroid withdrawal and also the patients in whom it was possible subsequently to achieve a useful reduction of dose. Case 1, whose symptoms did not recur until 10 weeks after withdrawal also belonged to group I. In contrast, group III represented those whose symptoms recurred so intensely that treatment had to be reintroduced within one week of withdrawal.

The values for Hb and total serum iron binding capacity did not reflect the underlying activity of the disease as judged by the ESR or PV (Table 3). The changes in WBC probably reflect the action of corticosteroids which can induce a leucocytosis (Nelson *et al.*, 1952; Floyd *et al.*, 1969). The mean serum iron value fell during the period of increased activity but the changes were not significant.

Several authors have recorded a raised alkaline phosphatase in PMR and some have produced evidence that this is related to arteritis in the liver (Heptinstall *et al.*, 1954; Palmer and Michael, 1965). The rise in alkaline phosphatase has been reported to return to normal with corticosteroid therapy (Hamilton *et al.*, 1971; Glick, 1972; Hall and Hargreaves, 1972). Only one of our patients showed a similar sequence. On withdrawal of corticosteroids a rise from 7 to 17 units was observed, returning to 7 when prednisolone was reintroduced.

Gradual withdrawal of corticosteroids has been studied by Bacon *et al.* (1966) in 35 patients suffering from rheumatoid arthritis. In spite of careful step-wise reduction (1 mg every 3½ months) the process had to be stopped in 24 patients owing in all but one of them to a flare-up of rheumatoid arthritis confirmed by objective clinical and laboratory findings. Only in our group I patients in period E did it seem that the rate could have been faster in PMR than in rheumatoid arthritis.

One of our patients was clinically and biologically controlled by intermittent therapy with prednisolone, 10 mg twice a week. Such a regimen would not depress the hypothalamo-pituitary adrenal axis to the same extent as daily divided doses (Ackerman and Nolan, 1968; Carter and James, 1972), and would also reduce the frequency of the other side effects (McGregor *et al.*, 1969; Siegel *et al.*, 1972). But in the controlled study by Hunder *et al.* (1975) only 6 out of 20 patients with active giant cell arteritis had their symptoms, including polymyalgia rheumatica, adequately suppressed on an alternate day therapy.

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References

- Ackerman, G. L., and Nolan, C. M. (1968). Adrenocortical responsiveness after alternate day corticosteroid therapy. *New England Journal of Medicine*, **278**, 405-409.
- Bacon, P. A., Myles, A. B., Beardwell, C. G., Daly, J. R., and Savage, O. (1966). Corticosteroid withdrawal in rheumatoid arthritis. *Lancet*, **2**, 935-937.
- Bagratuni, L. (1963). Prognosis in the anarthritic rheumatoid syndrome. *British Medical Journal*, **1**, 513-518.
- Brak, M. I. (1967). Articular and vascular manifestations of polymyalgia rheumatica. *Annals of the Rheumatic Diseases*, **26**, 103-116.
- Carter, M. E., and James, V. H. T. (1972). Effect of alternate day, single dose, corticosteroid therapy on pituitary-adrenal function. *Annals of the Rheumatic Diseases*, **31**, 379-383.
- Dixon, A. St. J. (1969). Polymyalgia rheumatica. *Textbook of the Rheumatic Diseases*, 4th ed., pp. 626-631. Ed. by W. S. C. Copeman. Churchill Livingstone, Edinburgh.
- Dixon, A. St. J. (1970). Polymyalgia rheumatica and giant cell arteritis. *British Medical Journal*, **4**, 235-236.
- Dixon, A. St. J., Beardwell, C., Kay, A., Wanka, J., and Wong, Y. T. (1966). Polymyalgia rheumatica and temporal arteritis. *Annals of the Rheumatic Diseases*, **25**, 203-208.
- Easterbrook, W. M., Baxter, D. W., and Martin, J. R. (1967). Temporal arteritis developing during indomethacin therapy of polymyalgia rheumatica. *Canadian Medical Association Journal*, **97**, 296-299.
- Esselinckx, W., Bucknall, R. C., and Dixon, A. St. J. (1977). Polymyalgia rheumatica—assessment of disease activity using the erythrocyte sedimentation rate and plasma viscosity. *Annals of the Rheumatic Diseases* (in press).
- Floyd, M., Muckle, T. J., and Kerr, D. N. S. (1969). Prednisolone induced leucocytosis in nephrotic syndrome. *Lancet*, **1**, 1192-1193.
- Glick, E. N. (1972). Raised serum alkaline phosphatase levels in polymyalgia rheumatica. *Lancet*, **2**, 328.
- Good, T. A., Benton, J. W., and Kelley, V. C. (1959). Symptomatology resulting from withdrawal of steroid hormone therapy. *Arthritis and Rheumatism*, **2**, 299-321.
- Gordon, I. (1960). Polymyalgia rheumatica—a clinical study of 21 cases. *Quarterly Journal of Medicine*, **29**, 473-488.
- Hall, G. H., and Hargreaves, T. (1972). Giant cell arteritis and raised serum alkaline phosphatase levels. *Lancet*, **2**, 48.
- Hamilton, C., Shelley, W., and Tumulty, P. (1971). Giant cell arteritis, including temporal arteritis and polymyalgia rheumatica. *Medicine (Baltimore)*, **50**, 1-27.
- Hargreave, F. E., McCarthy, D. S., and Pepys, J. (1969). Steroid 'pseudorheumatism' in asthma. *British Medical Journal*, **1**, 443-444.
- Heptinstall, R. H., Porter, K. A., and Barkley, H. (1954). Giant cell (temporal) arteritis. *Journal of Pathology and Bacteriology*, **67**, 507-519.
- Hunder, G. G., Sheps, S. G., Allen, G. L., and Joyce, J. W. (1975). Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis (comparison in a prospective study). *Annals of Internal Medicine*, **82**, 613-618.
- Livanou, T., Ferriman, D., and James, V. H. T. (1967). Recovery of hypothalamopituitary adrenal function after corticosteroid therapy. *Lancet*, **2**, 856-859.
- McGregor, R. R., Sheagren, J. H., Lipsett, M. B., and Wolff, S. M. (1969). Alternate day prednisone therapy—evaluation of delayed hypersensitivity responses, control of disease and steroid side effects. *New England Journal of Medicine*, **280**, 1427-1431.

- Mowat, A. G., and Hazleman, B. L. (1974). Polymyalgia rheumatica—a clinical study with particular reference to arterial disease. *Journal of Rheumatology*, **1**, 190–202.
- Myles, A. B. (1975). Polymyalgia rheumatica and giant cell arteritis. (Abst.) *Scandinavian Journal of Rheumatology*, Suppl. 8.
- Nelson, D. H., Sandberg, A. A., Palmer, J. G., and Tyler, F. H. (1952). Blood levels of 17 hydroxycorticosteroids following the administration of adrenal steroids and their relation to levels of circulating leucocytes. *Journal of Clinical Investigation*, **31**, 843–849.
- Palmer, H. P., and Michael, I. F. (1965). Giant cell myocarditis with multiple organ involvement. *Archives of Internal Medicine*, **116**, 444–447.
- Paulley, W., and Hughes, J. P. (1960). Giant cell arteritis of arteritis of the aged. *British Medical Journal*, **2**, 1562–1567.
- Paulsen, S., and Iversen, T. O. (1971). Rheumatic polymyalgia. Long-term treatment with steroids. *Acta Rheumatologica Scandinavica*, **17**, 165–168.
- Robinson, B. H. B., Mattingly, D., and Cope, C. L. (1962). Adrenal function after prolonged corticosteroid therapy. *British Medical Journal*, **2**, 1579–1584.
- Siegel, R. R., Luke, R. G., and Hellebusch, A. A. (1972). Reduction of toxicity of corticosteroid therapy after renal transplantation. *American Journal of Medicine*, **53**, 159–169.
- Wadman, B., and Werner, I. (1967). Therapeutic hazards of phenylbutazone and oxyphenbutazone in polymyalgia rheumatica. *Lancet*, **1**, 597–598.