Corticosteroids in the treatment of infectious mononucleosis

An assessment using a double blind trial

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INFECTIOUS mononucleosis is a disease which occurs in late adolescence and may adversely affect university students in their work and examination performance. It produces a variety of clinical pictures from a subclinical, symptom free state to a long relapsing course with considerable morbidity. On very rare occasions it may be fatal.

No satisfactory treatment has ever been established although corticosteroids have been used and reported upon from time to time.[1 2 3 4]

Only two double blind trials have been carried out to assess the value of steroids in the treatment of this disease; both of these were in the USA.[5 6] Neither of these investigations was entirely satisfactory in design and the use of steroids in infectious mononucleosis is still debatable.

The object of the investigation was to determine whether prednisone in a 6 or 12 day course was better than aspirin in both producing an immediate clinical and haematological improvement and preventing relapse later. Patients were seen at specified intervals after the infection for one year to assess progress.

Procedure

Participants

The patients were drawn from a student population of 5,000 looked after by the University Health Service, which has purpose-built premises with an inpatient unit of 20 beds and full-time nursing staff.

There were three physicians practising from the centre and all patients considered suitable for the trial were referred to the author.

Strict criteria had to be observed before patients were admitted to the trial because of the use of steroids and also the long surveillance intended. Only first or second year students who were in good health before the onset of the present illness were included. They had to be neither penicillin nor aspirin sensitive and to have no history of indigestion or past history of relevance. Because of the difficulties in assessing different methods of treatment, if started at varying times during the illness, all the patients were admitted to the trial on clinical suspicion of the illness and before they had been given any other treatment.

On admission to the trial and at each attendance, a routine clinical examination was followed for each patient and a note made of the condition of such factors as the throat, glands, and spleen on a standard record sheet.

An assessment of the psychological disturbance, so often an important feature in this illness, was obtained by the use of a short questionnaire. Patients were asked to mark how they felt on a linear scale relating to depression, lethargy, concentration, academic work and short temperedness. Scores were marked out of 50 and with patients acting as their own controls the nearer the score to 50 the nearer to 'normal' they became.

Laboratory investigations

All patients had haematological and serological tests done at regular intervals.

These tests were Hb, WBC, and differential count, ESR (Westergren), a heterophile antibody test and liver function tests, including SGOT, LDH and alkaline phosphatase. Throat swabs were taken for culture. All investigations were done in the pathology department of the Nottingham General Hospital.

In view of the recent interest in the EB virus, serum was taken for this titre at the same time as the other investigations. The titres were measured by the Virus Research Unit at Colindale. These results were not used in assessing whether patients were suffering from infectious mononucleosis in view of the current uncertainty about the relationship between the EB virus and clinical infectious mononucleosis. The heterophile antibody test was done by the standard method using Davidson's modification of Paul Bunnell's original method.

The laboratory findings were reviewed three months after the clinical diagnosis of the patients and the diagnosis was only confirmed if two of the following were present:

1. The patient was clinically suffering from infectious mononucleosis with generalised lymphadenopathy, general malaise, a sore throat, or splenomegaly.
2. The heterophile antibody test became positive during a period of three weeks.
3. The differential white count and abnormal mononuclear cells were highly suggestive of infectious mononucleosis.

The fact that four patients were included who did not have positive heterophile antibody tests should be explained. Some authorities would claim that no patient should be included who did not have a positive heterophile antibody test. The four cases in which this was negative were included for the following reasons:

Case 10 was clinically typical of infectious mononucleosis with sore throat, generalised lymphadenopathy and pyrexia on admission 38·3°C. Haematologically the evidence was very suggestive; two consultant haematologists supported this diagnosis, and the heterophile antibody test became weakly positive on one occasion.

Case 13 was strongly suggestive clinically and haematologically and had a doubtful heterophile antibody test on one occasion. Splenomegaly was also found.

Case 12 was very suggestive of the rather low grade and relapsing type of infectious mononucleosis and again two consultant haematologists confirmed the findings.

Finally, in case 24, clinically and haematologically this was felt to be infectious mononucleosis and the EB titre became very strongly positive.

Inevitably, starting treatment on making a clinical diagnosis and before haematological confirmation resulted in the treatment of a few patients who were later not definitely proved to have infectious mononucleosis. These had to be excluded from the final results.

Treatment

On admission to the trial each patient was allocated, using random numbers, to one of three courses of treatment. All three courses were identical in duration and appearance, consisting of white capsules taken for 12 days. On breaking the code, the courses were found to be made up as follows:

Days	1 & 2	3 & 4	5 & 6	7 & 8	9 & 10	11 & 12
Course A (aspirin)	600 mg, qds	600 mg, tds	600 mg, bd	300 mg, tds	300 mg, bd	300 mg, daily
Course B (prednisone)	10 mg, qds	10 mg, tds	10 mg, bd	5 mg, tds	5 mg, bd	5 mg, daily
Course C (prednisone days 1–6)	5 mg, qds	5 mg, tds	5 mg, bd	lactose, 1 tds	lactose, 1 bd	lactose, 1 daily

Neither doctor nor patient knew which course was A, B or C until the code was broken. All patients had concurrently a 12-day course of phenoxymethyl penicillin 250 mg qds. This was partly to remove any risk associated with a possible β haemolytic streptococcal infection and partly to avoid any possibility of superadded infection in case the patient was taking prednisone.

All patients considered suitable for admission to the trial readily agreed to co-operate after explanation. Steroid cards were not issued.

Each patient was admitted to a bed in the unit until his temperature was normal and he felt well enough to return to normal activities. Regular clinical examinations were made at intervals of 3 days, 6 days, 12 days, 3 weeks, 12 weeks, 24 weeks, 36 weeks and 52 weeks or as near to these intervals as possible allowing for vacations. Blood tests were taken on admission and at the above intervals. Extra tests were done between these intervals if particularly abnormal findings were discovered or if there was any suggestion clinically of a relapse. The temperature was recorded twice daily during admission.

General management of inpatients consisted of several days of partial bed rest combined with normal nursing care. Emphasis was laid upon early mobilisation and an encouragement to return to normal activities as quickly as possible, because prolonged bed rest in one of the American series was shown to slow down the rate of return to full recovery.[7] If the liver function tests were markedly abnormal, patients were advised to refrain from alcohol for at least a month.

TABLE I

Course	*Case No.*	*No. of days to normal temp.*	*No. of days to normal* WBC	*No. of days to neg. heterophile antibody*	*EBV titre*	*No. of days for psych. score* 45
A	1	0	21	84	positive	0
	2	7	84	84	positive	12
	3	6	84	168	positive	21
	4	2	42	84	positive	84
	5	3	12	84	positive	84
	6	4	42	168	positive	21
	7	11	42	84	positive	84
	8	3	84	84	positive	252
	9	17	42	84	positive	6
	10	7	42	Always neg.	negative	84
B	11	1	6	42	positive	21
	12	2	21	Always neg.	negative	84
	13	1	6	Always neg.	negative	84
	14	1	21	21	positive	21
	15	3	42	84	positive	0
	16	1	21	42	positive	21
	17	7	42	42	positive	84
	18	1	21	42	positive	21
	19	2	42	42	positive	21
C	20	14	21	42	positive	21
	21	14	21	84	positive	84
	22	0	21	42	positive	0
	23	4	42	168	positive	21
	24	1	6	Always neg.	positive	21
	25	0	21	84	positive	42
	26	1	12	6	positive	21

Results

Thirty-eight patients were admitted to the trial and allocated to either course A, B or C. Of these 38, 12 were rejected during subsequent months leaving 26 cases for final analysis. The reasons for rejection will be discussed later. The 26 cases whose investigations lasted a year were found to have been allocated to courses A, B and C in the ratio 10: 9: 7.

The sex distribution was as follows: course A, five males and five females; course B, four females and five males; course C, two females and five males.

While clinical symptoms such as sore throat were noted on admission it was not intended to investigate the effects of steroids upon these symptoms, as this has been done by other authors.[5]

The mean temperature of patients on course A on admission was 38·3°C, of those on course B was 38·2°C and of those on course C, 37·8°C. Patients on all the courses had on average three groups of lymph glands enlarged when first examined and all had symptoms of general malaise and sore throat. An attempt was made to measure the level of malaise using the questionnaire mentioned above and scoring the results out of 50 points.

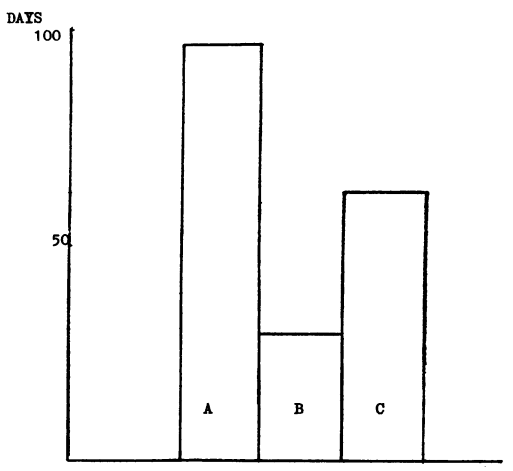

Figure 1: Number of days to negative heterophile antibody test.

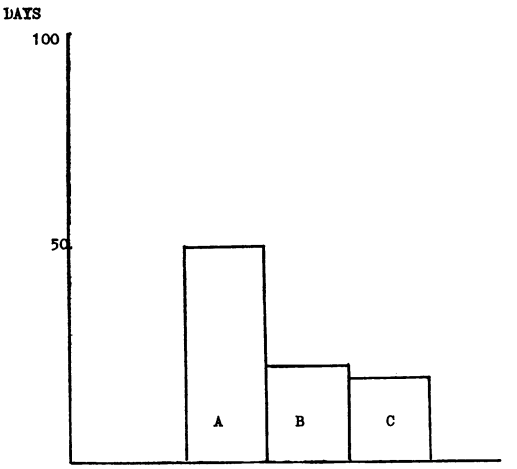

Figure 2: Number of days to normal psychiatric score.

Figures 1, 2, 3, 4 and 5 show the effect of courses A, B and C on the length of time taken for the temperature, the psychiatric score, the white count, the heterophile antibody test and the ESR to return to normal.

Table I shows these results in detail and also includes the results of the EB virus titres.

Using the 'Wilcoxon' non parametric test for small samples the following results were obtained:

1. Comparison of course A with courses B and C (Table II).
2. Comparison of course B with course C.

   From the statistical evidence it is impossible to show that there is any reduction in the return to normal achieved by course B when compared with course C. One would expect this result from figures 1, 2 and 3.
3. (a) Comparison of other criteria with temperature in the three courses (Table III).

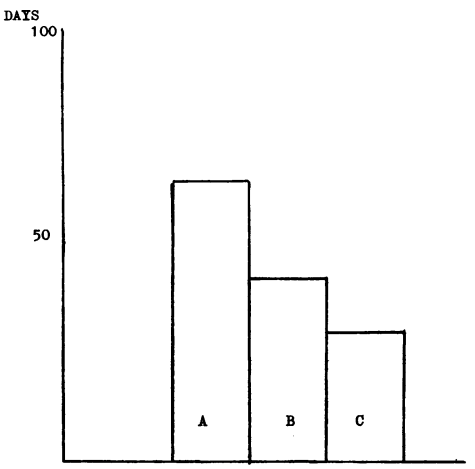

Figure 3: Number of days to normal WBC.

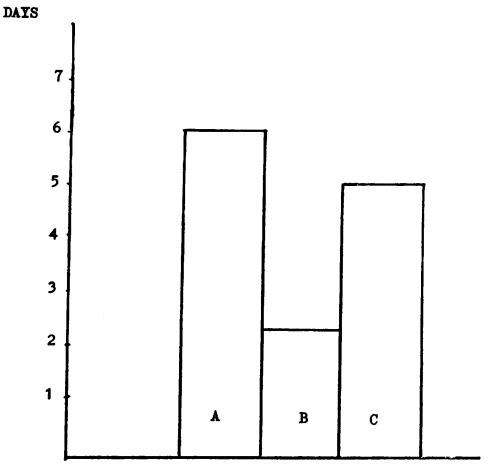

Figure 4: Number of days to normal temperature.

TABLE II
COMPARISON OF COURSE A WITH COURSES B AND C

Measure	*Course B*	*Course C*
Temperature	Significant p=0.05	Not significant
GF cell count	Significant p=0.025	Significant p=0.025
Neg. heterophile antibody titre	Significant p=0.005	Not significant
Psychiatric score	Not significant	Not significant

Deduction: Course B will reduce the length of time for the return to normal of temperature, G.F. cells and P.B. titre but has no effect on the psychiatric score. There is a reduction in the time taken for the psychiatric score in courses B and C to return to normal, but this is not sufficient to be significant (*see* Figure 2).

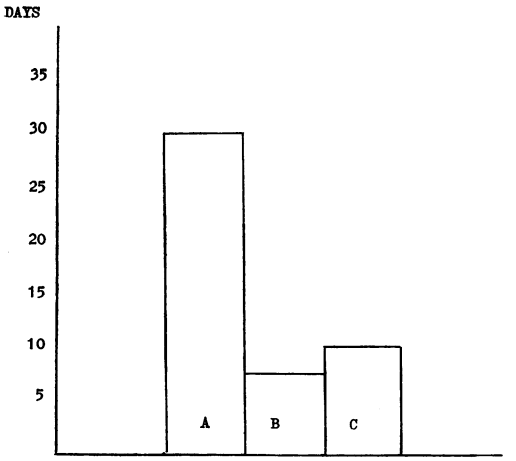

Figure 5: Number of days for ESR to fall below 10mm/hr.

TABLE III

Temperature measured against:	*G.F. cell*	*Heterophile antibody titre*	*Psychiatric score*
Course A	No correlation	No correlation	No correlation
Course B	Correlation p=0.01	No correlation	No correlation
Course C	No correlation	No correlation	No correlation
Total	Correlation p=0.05	No correlation	No correlation

Deduction: The only significant result appears to be between temperature fall and the rate of return to normal of the white cell count by patients taking course B.

(b) Comparison of return to normal of G.F. cell count and return to normal of heterophile antibody and psychiatric score.

TABLE IV

G.F. Cell Count against:	*Heterophile Antibody titre*	*Psychiatric score*
Course A	No Correlation	No Correlation
Course B	Significant p=0.01	No Correlation
Course C	Significant p=0.01	No Correlation
Total	Significant p=0.05	No Correlation

Deduction: A significant correlation is shown between the G.F. cell measure and the return to negative of the heterophile antibody in all patients receiving treatment with courses B and C.

To summarize the above findings, it can be shown statistically that prednisone reduces the time for the haematological findings and the temperature to return to normal. There is also a statistical correlation between the rate of return to normal of the temperature, G.F. cell count and the heterophile antibody titre.

Lymphadenopathy

No relationship was found clinically or in the blood tests between the number of glands enlarged and the course of the illness. Many patients still had a few glands palpable one year later, often cervical, sometimes axillary; although they felt well in all respects and their blood tests were normal. Because the palpation of glands is so subjective, even when done by one observer only, it was impossible to note any relationship between treatment and demonstrable decrease in glandular enlargement.

Splenomegaly

This was noted in four cases, namely 9 (course A), 13, 18 (course B) and 21 (course C). Only in the latter did this persist for more than a few days. In case 21 it was noted for 21 days.

β *Haemolytic streptococcal infection*

Positive throat swabs were obtained in four cases, namely 9, 19, 21 and 25. This infection was also responsible for the original misdiagnosis in seven of the 12 cases rejected on review of the original 38 patients admitted to the trial.

Liver function tests

Abnormal liver function tests, particularly enzyme tests, have often been noted in this illness. This was confirmed in this investigation and 18 out of 26 cases had an

LDH above 200 when first seen. However the other liver function tests which were not so sensitive, e.g. serum bilirubin, were only marginally raised in the four cases in which they were abnormal. The enzyme levels fluctuated so widely during the first three weeks of the illness and so many other factors might have been involved, with tissues other than the liver being affected, that it was decided to ignore these findings in assessing the value of treatment. There was no relationship between the rate of fall of the LDH and any of the courses of treatment.

ESR

An ESR of more than 20 mm/hr (Westergren) was noted in only five cases on admission. In two of those treated with aspirin it persisted at a high level for six and 24 weeks respectively.

Figure 5 shows the average length of time taken for the ESR to fall below 10 mm/hr.

Withdrawn cases

Twelve cases started treatment but were withdrawn from the trial before surveillance was completed. Seven of these had a β haemolytic streptococcal infection and, as already mentioned, this is a common cause of mistaken diagnosis. In three cases no cause for their symptoms was ever isolated and in two cases they had infectious mononucleosis but defaulted from surveillance despite repeated requests to attend for examinations.

Discussion

Controversy has arisen over the value of corticosteroids in the treatment of infectious mononucleosis. Some authorities have maintained that this was a dangerous treatment and that it ought to be witheld except in the very rare life endangering situation.[3 8 9 10 11]

Other authorities,[12 4] particularly in the USA, have favoured the use of corticosteroids in virtually all cases. In the double blind trials carried out there, the patient was given corticosteroids if slow to respond to the trial treatment.[5 6]

A great deal of interest has been aroused during the last two years about the relationship between the abnormal appearance of the monocytes in infectious mononucleosis and the appearance of the white blood cells in the early stages of leukaemia. One of the criticisms levelled at the use of steroids has been that they interfered with immune mechanisms and, might predispose the patient to leukaemic changes. There has been no evidence that this is so.

All cases treated with steroids, for whatever reason, must be carefully supervised but there has been no evidence in the literature, or from personal experience, that in selected cases a starting dose of 40–60 mg of prednisone tailing off over about ten days produces unacceptable side effects or risks.

In this study cases were selected on the basis of previous good health and no specific contra-indications to steroid treatment and were supervised as if they were all taking prednisone.

It was found that a β haemolytic streptococcal infection was often present in cases of infectious mononucleosis and was also the commonest cause of confusion in diagnosis when the patient was originally seen.

The results showed that prednisone significantly increased the rate at which the temperature fell, the white cell count returned to normal and the heterophile antibody titre reverted to negative in cases treated with a 12-day course of prednisone compared with aspirin when both groups were also taking penicillin. As might be expected, the six-day course of prednisone showed no significant difference from aspirin except in the rate at which the blood film returned to normal.

The rate at which haematological factors return to normal in those taking prednisone

may account for the feeling of well-being which patients treated in this way often have. An attempt was made by means of a simple questionnaire to measure the degree of depression and lethargy. Figure 2 shows that patients on courses B and C returned to a normal state more rapidly. Unfortunately many other factors affect emotional levels so that this may not be an entirely reliable measurement of progress.

One of the aims of this study and the long surveillance was to investigate the incidence of relapse and see if treatment had any effect upon this. If people were made to feel better by prednisone due to temporary suppression of an immune reaction, then one would expect a high incidence of relapse in courses B and C. In fact, there was only one genuine and haemotologically proven case of relapse and that was in someone treated with aspirin (case 3, table I).

Case 23 on course C, developed a recurrence of symptoms about five days after finishing the six-day course of prednisone suggesting that his symptoms had been only partially suppressed by an inadequate dose. His symptoms lasted for a further week.

The high morbidity normally associated with this illness[12] was not substantiated irrespective of the type of treatment and it appears that it is very easy to blame any future ill health, particularly the rather vague complaints so prevalent in general practice, upon a previous episode of infectious mononucleosis with no real evidence to support this.

Liver function tests were often abnormal. They were variable in level and tended to fluctuate widely in the same patient on different occasions. No relationship could be shown between the type of treatment and these tests.

Detailed clinical observations were recorded on all patients at each attendance but apart from a general guide to how the patient felt there was no relationship with haematological findings or progress. Many patients felt very well with marked lymphadenopathy. Conversely some patients were still feeling tired and unwell even when there was little abnormal to be found.

Splenomegaly was noted in four cases, which is a slightly lower percentage than reported by most observers (15 per cent). Starting treatment quickly with prednisone may have suppressed splenomegaly before it was clinically demonstrated.

Conclusion

In this double blind trial it has been shown that a 12-day course of treatment with prednisone, starting at a total daily dose of 40 mg and reducing gradually, has a significant effect on the course of the illness in patients suffering from infectious mononucleosis. Despite the small number of cases involved, a statistically significant rate in the return to normal of the temperature, differential white cell count and heterophile antibody test was found, with a more rapid improvement in the symptoms of these cases. There appeared to be little measureable effect on the rate of regression of lymphadenopathy in any of the courses of treatment.

From the evidence, the six-day course of prednisone was not enough to produce improvement when compared with aspirin.

Thus in considering the treatment of a case of infectious mononucleosis it would be reasonable, in the absence of contra-indications to steroids, to consider the use of these with a starting dose of about 40 mg prednisone (or the equivalent) reducing over 12 days. No other study has adequately demonstrated these facts.

Summary

A double blind trial has been described in which the effects of treatment with either aspirin or prednisone has been compared in 26 patients suffering from infectious mononucleosis. Cases have been followed up for one year.

It has been shown that a 12-day course of prednisone in a decreasing dosage is significantly better than aspirin and it is suggested that a short course of steroids should always be considered for patients with infectious mononucleosis.

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ADDENDUM

Dr Bolden is now working in general practice in Exeter.

PSYCHIATRIC SOCIAL WORKERS IN GENERAL PRACTICE

This paper reports an experimental part-time attachment of a psychiatric social worker to a London general practice of three principals, two of whom took part in the selection of cases for referral to the psychiatric social worker. It was limited to a period of six months, and to only six patients, one of whom proved to be schizophrenic and was referred on to a consultant psychiatrist on failing to respond to therapy. During the same period, the practice selected four other cases of psychosis for referral direct to a psychiatrist. On this rather flimsy evidence the writers conclude that psychiatric social worker attachments to general practices would reduce the referral rate to psychiatrists by 50 per cent.

Be this as it may, the paper adds a modest contribution to the now considerable literature reporting experience of caseworker-trained social workers in harness with general practitioners. Most report important improvements in the psychosocial service of the practices concerned. Criteria of success for the general practitioner caseworker teams are open to criticism in this paper, as they have been in other reports, but the writers share the confidence of most other workers reporting on the importance of this approach in developing better diagnosis and care of psychosocial illness at home. This is a large area of general practice today.

The writers' report greatest success with their depressive patients, some success with personality disorder, and no therapeutic effect on the schizophrenic patient.

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