The results of our present trial suggest that there may be little important difference between three-day and 10-day courses of amoxycillin. Within the sample of patients we studied a number undoubtedly had a self-limiting disease which required no antibiotic treatment at all. There may also have been a group for whom three-day or even 10-day treatment would have been inadequate. We cannot, in retrospect, identify any of these groups. Nevertheless, most of the improvement in symptoms clearly occurs in the first few days. We suggest that patients with otitis media who need antibiotics should be treated for three days only and then reassessed at about the fifth or sixth day after starting treatment. Only those whose rate of improvement is unsatisfactory should have antibiotics for longer. The relatively high frequency of hearing loss in both groups three months after an episode is not unexpected and emphasises the need to follow up these patients until hearing returns to normal. We have shown that this form of management is practicable in British general practice and could save the Health Service over £1 million annually in antibiotic costs without reducing the standard of care.

Whether overall savings would result from this policy can be determined only by a full cost-benefit analysis, which we have not attempted.

We thank Mr J B Booth and Mr S J Abramovich, who acted as independent assessors of the audiograms. We gratefully acknowledge the generous financial support from the special trustees of the London Hospital, without whom this trial could not have taken place. We also thank Messrs Edwin Burgess for sensible graduated 2-5 ml plastic spoons and Messrs Bencard for trial supplies.

**Survival and desferrioxamine in thalassaemia major**

**B MODELL, E A LETSKY, D M FLYNN, R PETO, D J WEATHERALL**

**Abstract**

A small randomised trial and observation of all patients homozygous for beta-thalassaemia in Britain born in or before 1963 indicated that those patients who had received average weekly doses of more than 4 g of desferrioxamine over the previous few years were less likely to die in the near future than were patients of similar ages who had received less, or no, desferrioxamine.

**Introduction**

Patients homozygous for β-thalassaemia die of anaemia in infancy unless regularly transfused. Each unit of blood contains about 200 mg of iron, however, so that patients treated only by regular transfusion usually die in their second or third decade from the chronic effects of iron deposited in the myocardium. Early attempts to control iron overload by daily intramuscular injection of the iron-chelating agent desferrioxamine showed that iron excretion would balance iron input only when the concentration of iron in the body was undesirably high.1-4 When the drug is administered by slow subcutaneous infusion, however, a given dose is more effective and larger doses may be used; hence this approach may more successfully control iron overload.1-9 Regular parenteral infusion of desferrioxamine is cumbersome and expensive, and it is therefore desirable to know whether iron-chelation treatment measurably alters the survival of patients with transfusion-dependent β-thalassaemia. In British children with β-thalassaemia major we were first given desferrioxamine in 1962, and since 1967 some have received daily intramuscular injections amounting to an average of about 4 g a week, in the hope of postponing or even preventing cardiac death.4 The numbers of children treated with desferrioxamine have increased steadily, though many at first received the drug only intravenously at the time of transfusion or in infrequent short intramuscular courses that would not be expected to achieve a net iron balance in a transfusion-dependent child. In the late 1970s, as a result of the gradual accumulation of evidence for its value, practically all patients in Britain had begun regular subcutaneous infusions of desferrioxamine.

We present details of drug doses and survival for all patients

---

**References**


(Accepted 24 February 1982)
homozygous for \( \beta \)-thalassaemia in Britain since desferrioxamine began to be used. Our chief aim was to determine whether those patients who had been given the drug regularly for several years were any less likely to die in the immediate future than were patients of similar age who had received less, or no, desferrioxamine.

Patients

Patients with thalassaemia who are regularly transfused do not die of iron overload before 10 years of age. Hence, and because desferrioxamine became available for clinical use in Britain only in 1963, we followed up to the end of 1980 all children with thalassaemia major who were born in or before 1963 and who were alive and resident in Britain on their tenth birthday.

For the 92 such patients dates of birth and death and number of grams of desferrioxamine given in each calendar year from 1963 to 1978 were abstracted from medical records. (These data are listed in an appendix, which along with a statistical appendix may be obtained on request from DJW.) The patients were located in the following three ways.

1. In 1967 we searched the diagnostic indexes of all London hospitals that treat children and investigated all mentions of thalassaemia added to diagnostic indexes over the next 10 years to ensure complete coverage of the London area, where most Mediterranean immigrants live.

2. In 1975 members of the British Paediatric Association were circulated asking for brief details of all living children with thalassaemia. We think that full co-operation was achieved, and a subsequent approach to all members of the British Society for Haematology yielded no cases that had not been ascertained through the first two channels.

3. Finally, the Registrar General provided a list of all deaths with any mention of thalassaemia in the years 1963-77. Informal information on such deaths is now also provided by the UK Thalassaemia Society (a patients' and parents' association).

If, as we think likely, our coverage was complete or virtually complete then no bias was introduced by selecting patients because they were alive in 1975 or because they had died and been registered, and we had abstracted data from the patients' medical records. Though small, these two groups were interesting because comparison was definitely unbiased and there was a very pronounced contrast in the dosage of the drug given to the two groups, the treated patients having received about 4 g weekly for over 10 years.

The remaining 73 patients were not in the randomised trial and the decision to give desferrioxamine depended on the paediatrician. Many were not given the drug at all for as long as their health appeared sound, and some received inadequate doses, usually less than 1 g/week given in the blood at transfusion; but with the passage of time an increasing number—even when in good health—received larger doses nearly comparable to those used in the randomised trial, though for fewer years.

It is obviously more difficult to interpret non-randomised data than the results of a randomised trial. The only important bias that we knew of in the non-randomised group was that as patients who received little or no desferrioxamine developed serious symptoms of iron toxicity they tended to be given very large doses of the drug in the year or so before their death, and unless this tendency is allowed for it might misleadingly appear to starting the drug is extremely dangerous. A preliminary survey of the complete data showed no significant differences in transfusion scheme or splenectomy rate between the group who had received little or no desferrioxamine and the group who had received daily intramuscular injections. We therefore doubt whether physicians who prescribed to use the drug were either more or less vigorous or skilled in other aspects of their general management of these children, or whether they were influenced in their decision to use or not use the drug by any clinical observations that would be relevant to future cardiac death in apparently healthy patients with thalassaemia. If this were the case simple comparison of mortality in the patients who had received regular treatment with the drug and those who had not should yield a relatively unbiased measure of the benefit of desferrioxamine, even though allocation to treatment was not properly randomised.

Methods

At the beginning of each year (1963-80) we computed for each patient a "mean desferrioxamine index." This was the mean weekly dose of the drug that the patient had received in the first five of the six preceding years (fig 1). The mean index was then related to the likelihood of death in the following year using the statistical methods described in the appendix (with correction for continuity). Three points should be made about this index. Firstly, it ignores desferrioxamine given in the immediate past year for terminally ill patients. Secondly, it assesses usage of the drug over a relatively long period, because iron deposition reaches an equilibrium, and is therefore less likely to change the tendency for the drug to be used more widely patients aged 15-20 in 1980 were likely to have a higher mean index than were patients aged 15-20 in, say, 1970; hence any general improvement in medical care over the 10 years which reduced the likelihood of death may masquerade as an advantage of desferrioxamine when we come to interpret the non-randomised data. Nevertheless, this bias is less severe than might be expected because the immigrant groups among whom this disease occurs is such that only three deaths from iron overload occurred in the early period 1963-5, whereas the remaining 22 deaths among the non-randomised patients occurred in 1970-80.

Statistical—All p values cited here are "one tailed"—that is, they estimate the probability of at least as great a difference in mortality in favour of desferrioxamine appearing by chance alone. Doubling the 1p values gives the more usual two-tailed p value which estimate the probability of at least as great a difference in one direction or the other arising by chance alone.

Results

OVERALL SURVIVAL, IRRESPECTIVE OF TREATMENT

By pooling all the available data we used standard methods11 to construct a life table which describes the age-specific mortality of the entire group of patients (fig 2).

RANDOMISED TRIAL

In 1966-7 at the Hospital for Sick Children, London, 20 patients thought to have thalassaemia major were randomised between a regimen including an average of about 4 g desferrioxamine weekly and a control regimen not including the drug. In one patient (allocated to the drug and who started the well) the diagnosis was later changed to thalassaemia intermedia, leaving 10 control patients (born on average in 1959), six of whom had died by 1980, and nine treated patients (born on average in 1960), only one of whom had died by 1980. (The patient who died differed from the rest of the treated group in having moved to another hospital four years before his death, where he received less frequent transfusions than the other patients; he also had diabetes.) All seven deaths occurred in patients with a history of iron overload. The results of the statistical analysis (table 1) were promising but not conclusive (1p = 0.04 by Fisher's exact test; 1p = 0.07 by the age-standardised analysis (table 1 and statistical appendix)). This might have been due to the small size of the group.
and the fact that the treated patients had an average date of birth of 1960 and so were only just entering the period of greatest risk (see fig 2). If with continued follow-up their survival remained good for five more years (from 1980), this would provide stronger evidence for a real beneficial effect of desferrioxamine.

Two of the 13 deaths among patients who had not been treated with desferrioxamine were not associated with iron overload; however, and arguably these were irrelevant to our assessment of the drug. Even when the analysis was repeated with these two deaths excluded, however, a highly significant trend remained ($z = 2.58$ with correction for continuity; $p = 0.005$).

The choice of a six-year moving average to define the mean desferrioxamine index was made on prior theoretical grounds, independent of the actual data, but the exact number of years did not appear to be critical. For example, the statistical significance levels were, if anything, somewhat more extreme ($z = 3.91; p = 0.0007$) when a three-year moving average was used instead (so that the mean index was defined as the mean weekly dose in the first two of the three preceding years).

**Discussion**

The data available so far show significantly better survival among children for whom an average weekly dose of at least 3 g desferrioxamine was established, and, despite the various possibilities of bias that existed, the most plausible interpretation is that the treatment actually prevented or delayed several deaths. Theoretically there are two possible ways in which the drug might prevent disease due to iron overload. Firstly, on the assumption that disease is simply related to the total body iron load, the drug might protect simply by reducing this. If so, prolonged administration of high doses of desferrioxamine would presumably be needed to produce the requisite major change in iron load. Alternatively, considerably lower doses might in principle exert an antioxidant effect since desferrioxamine chelates the most labile, and therefore presumably the most toxic, iron fraction. Such an effect could be relatively independent of the total iron load and might be brought about by regular administration of relatively small doses. In both cases, however, treatment is likely to have to be given over at least a few years before any measurable benefit can be anticipated, for myocardial damage by iron is a chronic process and only slowly reversible, if it can be reversed at all.

Because of the uncertainty about the chief mechanisms of action of desferrioxamine theory alone cannot predict what will be an adequate dose. It is noteworthy that even among patients maintained for some years on average weekly doses of over 5 g three deaths occurred, all associated with iron overload, and such patients may also develop other abnormalities or growth disturbance. An important point is that the dose of desferrioxamine was not weight related in either the randomised or most of the non-randomised patients. In most patients the relative dose dropped steadily as the patients grew, so its effectiveness would be expected to decrease with age. For instance, in the randomised treated patients the range of doses was 15-28 mg/kg/day at the start of the trial and 7-14 mg/kg/day six years later. If, as it appears, such treatment does have a substantial effect on survival the final dose was so small as to suggest that the drug may indeed exert an antioxidant effect by chelating the most toxic iron fraction in addition to its effect on body iron load. Desferrioxamine at a dosage of 4 g/kg may delay the onset of hepatic fibrosis and reduce the incidence of cardiac arrhythmias. Our data suggest that this dosage can also prolong life, but it is not clear whether death is substantially delayed by such treatment, because most deaths occur between the ages of 15 and 25 years and the patients that have been treated with this sort of regimen are as yet only at about their 20th year. Practically all patients now receive higher doses of desferrioxamine by regular subcutaneous infusion, however, and so it will not be possible by further study of this group of patients to establish the final life expectancy of children treated intramuscularly alone.

What should be the policy regarding the management of homozygous 6-thalassaemia? It is now clearly established that using the newer techniques of the administration of desferrioxamine by subcutaneous infusion it is possible to achieve negative iron balance in older patients over a relatively long period and stabilise the body iron load of small children at a relatively low value. Moreover, there has been no evidence of tachy-

---

**TABLE I**—Age-standardised analysis of relevance of allocated treatment to risk of death in randomised trial at Hospital for Sick Children, London, 1966-80. (All seven deaths occurred in patients with a history of iron overload)

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths</th>
<th>Ratio O:E</th>
<th>Normalised test statistic for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (10 patients)</td>
<td>Expected (E)</td>
<td>Observed (O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.47</td>
<td>3.53</td>
<td>1.7 0.3</td>
</tr>
<tr>
<td>Treated (9 patients)</td>
<td>4.71</td>
<td>5.16</td>
<td>1.0 0.0</td>
</tr>
<tr>
<td>Both groups</td>
<td>7.00</td>
<td>7.12</td>
<td>1.0 0.0</td>
</tr>
</tbody>
</table>

*With correction for continuity. Cited p value for one-tailed test of statistical significance.

**TABLE II**—Age-standardised analysis of relevance of mean desferrioxamine index (MDI) in first five of six preceding years to risk of death during coming year. All 92 patients (19 randomised + 73 not)

<table>
<thead>
<tr>
<th>MDI range</th>
<th>Deaths</th>
<th>Ratio O:E</th>
<th>Normalised test statistic for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.59</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Up to 1 g/week</td>
<td>4.77</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Up to 2 g/week</td>
<td>3.08</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Up to 3 g/week</td>
<td>1.27</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>3 or more g/week</td>
<td>0.33</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32.00</td>
<td>32.00</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*With correction for continuity. Cited p value for one-tailed test of statistical significance. Expected numbers of deaths (here, as in table I) were standardised for single years of age, but not for calendar years.

"Two deaths in patients with no history of iron overload."
phylaxis, and there is also preliminary evidence for improvement in organ function in patients treated in this way. Thus where possible affected children should presumably be treated with desferrioxamine using the subcutaneous infusion approach or, if this is not practicable, by administering the drug intramuscularly at the dose of at least the 15-28 mg/kg/day achieved at the beginning of the study by Barry et al. Also the progress of the children treated in this way should be monitored with respect to age at onset of puberty, liver iron loading and function, endocrine and cardiac function, growth rate, and overall wellbeing. If really large effects on survival are produced by these more aggressive forms of chelation treatment they may hopefully be shown convincingly by simple comparison of future mortality with the data we report here. More moderate effects, however, might fail to be clearly recognised in such a non-random historical comparison and, of course, any general improvements in ancillary management may yield improved survival which is mistakenly attributed to infusions of desferrioxamine. Perhaps, however, these difficulties of interpretation will eventually be bypassed by introducing less troublesome methods of avoiding iron overload.

We gratefully record that we received 100% co-operation from the many clinicians looking after older thalassaemic patients in Britain. This work was supported by a Medical Research Council grant, and BM expresses appreciation of the personal help of Prince Sultan bin Abdulaziz, of Saudi Arabia, and the kindness of Madame Nouha and Sheikh Faisal Al-Hegelan.

The data and statistical appendices may be obtained on request from DJW.

References


(Accepted 8 January 1982)

SHORT REPORTS

Importance of short-term changes in glycosylated haemoglobin

Formation of glycosylated haemoglobin (haemoglobin A1b) has been considered to occur slowly within the erythrocyte at a rate dependent on the ambient blood glucose concentration. The amount formed has therefore been thought to reflect the average blood glucose concentration over the previous two to three months. Recent reports have shown, however, that acute reversible changes in glycosylation may occur and are related to short-term fluctuations in blood glucose concentration. These reports raise important questions concerning the validity of measurements of haemoglobin A1 as indicators of long-term diabetic control.

We examined the magnitude of these reversible changes, and their relation with the total proportion of haemoglobin A1b and blood glucose concentration, in an attempt to assess their importance in clinical practice.

Patients, methods, and results

The method for measuring the reversible, or labile, fraction (difference in percentage) of haemoglobin A1b was established by comparing the time course of changes in the percentage of haemoglobin A1b due to dissociation of this fraction during incubation for 24 hours in glucose-free medium (0-9% saline) at 4°C, 22°C, and 37°C. Blood was drawn from six diabetic inpatients and two normal subjects and was placed into EDTA. The proportion of haemoglobin A1b was assayed by a microcolumn method modified from that of Kynoch and Lehmann. At 37°C dissociation of the labile fraction appeared complete at 18 hours. At 22°C the fall in the percentage of haemoglobin A1b at 18 and at 24 hours did not differ appreciably from the fall at 37°C, whereas at 4°C no appreciable dissociation was seen.

In a larger study of 65 diabetic outpatients we took the magnitude of the difference in the percentage of haemoglobin A1b as the difference between the percentage of haemoglobin A1b measured after 18 hours’ incubation in saline at 4°C and 22°C. Blood was obtained by fingerprick, and two 50 μl aliquots were added immediately to 1 ml of 0-8% saline for subsequent measurement of percentage of haemoglobin A1b. A further aliquot was used for immediate estimation of blood glucose concentration. Percentage of haemoglobin A1b was measured using both the microcolumn method and electroendosmosis (Corning Medical Ltd). Good agreement between these two methods has been shown in this laboratory.

The figure shows the results of this study. Good agreement between the two methods was again seen. The difference in the percentage of haemoglobin A1b was relatively small (1-2 ± SD 0.9%), range –0.5 to 3.7; and 1-0 ± 0.7%, range –0-23 to 2-02 for the two methods respectively.

Comment

Our results confirm the presence of a reversibly bound labile component in the glycosylated haemoglobin fraction which can be removed by incubation in glucose-free medium for 18 hours at 22°C. In the diabetic patient this labile fraction produced a fall of approximately 1%, determined by both methods of measurement, in the percentage of haemoglobin A1b, though just occasionally the difference was greater. This suggests that removal of the labile fraction does not appreciably improve the clinical value of the results and does not justify the time and cost incurred in the additional manipulation of samples.

Measurement of the percentage of haemoglobin A1b is at its most useful in the diabetic clinic, when the result is available at the time that the patient is seen. Time spent in removing the labile fraction would preclude the availability of the result at the time of consultation, and the benefits obtained would not, in our opinion, justify the extra cost and effort. This immediate availability of results is possible only