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Poor response to treatment of renal anaemia with erythropoietin corrected by iron given intravenously

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Recombinant human erythropoietin is being used increasingly to treat renal anaemia in patients receiving haemodialysis and continuous ambulatory peritoneal dialysis. Its efficacy is undisputed; nevertheless, several centres have reported that some patients have responded poorly, slowly, or not at all. We report on five patients who responded poorly to such treatment until they were given iron intravenously.

Case reports

The five patients we describe participated in a study assessing the effect of erythropoietin on renal anaemia in 11 patients who were receiving regular haemodialysis. All five were treated with erythropoietin (Boehringer Mannheim) 240 U/kg/week intravenously and started prophylactic oral iron supplementation (ferrous gluconate 300 mg/day; 35 mg elemental iron) two weeks before the treatment with erythropoietin. Each patient had a normal serum ferritin concentration before treatment (51, 40, 44, 34, and 37 μg/l; normal range 15-300 μg/l). Serum iron concentration and total iron binding capacity were monitored and the percentage saturation with transferrin calculated (serum iron concentration (μmol/l)÷total iron binding capacity (μmol/l)×100%).

The mean (SD) increase in haemoglobin concentration in the five patients was 25 (13) g/l over the first eight weeks of treatment with erythropoietin compared with 45 (20) g/l in six other patients in the study (all of whom had serum ferritin concentrations >400 μg/l and transferrin saturations >30% before treatment). Each of the five patients had an initial rise in haemoglobin concentration, which was not sustained; they were then given iron dextran intravenously (Imferon; 50 mg elemental iron/ml) 1 ml twice weekly during the last hour of dialysis.

The mean weekly rise in haemoglobin concentration during the four weeks before intravenous treatment with iron was 2·0 g/l; this rose to 5·3 g/l after the treatment was started ($p<0·005$, paired t test), indicating more effective erythropoiesis even though the dose of erythropoietin was the same (table). Four of the patients had normal serum ferritin concentrations immediately before treatment with iron, suggesting adequate stores of iron in marrow; the remaining patient had a concentration at the lower limit of the normal range. In contrast, all five patients had low transferrin saturations (<20%).

Comment

Our data show a retarded response of haemoglobin concentration to erythropoietin, which was corrected by giving iron intravenously. Eschbach *et al* also reported on a patient in whom the response of the packed cell volume declined in the presence of an ample serum ferritin concentration (518 μg/l) but low transferrin saturation (13%); this patient also responded to intravenous treatment with iron dextran.[1]

Erythropoietin seems to stimulate erythropoiesis to such an extent that the demand for iron can exceed the body's ability to release it from stores. This may lead to a functional iron deficiency, which can occur when serum ferritin concentrations are normal and iron can be detected in the marrow by staining.

Previous studies have suggested that stores of iron are adequate for erythropoiesis only if for every 50 g/l rise in haemoglobin concentration a serum ferritin concentration of ⩾100 μg/l is present.[2] Patients who are particularly likely to develop functional iron deficiency, therefore, are those with serum ferritin

Clinical measurements in five patients receiving dialysis and treatment with erythropoietin before and after intravenous treatment with iron. Figures in parentheses are percentage transferrin saturations

Case No	Age (years)	Sex	No of weeks of treatment with erythropoietin when response was poor	Before intravenous treatment with iron: Weekly increase in haemoglobin (g/l)*	Serum ferritin (μg/l)†	Serum iron (μmol/l)/ total iron binding capacity (μmol/l)†	After intravenous treatment with iron: Weekly increase in haemoglobin (g/l)‡	Serum ferritin (μg/l)§	Serum iron (μmol/l)/ total iron binding capacity (μmol/l)§
1	26	M	5-7	2·3	16	4·8/54·0 (8·9)	8·0	17	23·2/59·8 (38·8)
2	51	F	4-8	1·8	35	5·0/57·5 (8·7)	3·5	56	20·0/53·3 (37·5)
3	22	M	2-6	0·3	32	7·8/44·4 (17·6)	3·8	21	47·0/53·3 (88·2)
4	53	M	3-6	2·3	14	6·7/54·0 (12·4)	4·8	30	17·5/56·5 (31·0)
5	52	M	2-6	3·3	31	8·5/50·6 (16·8)	6·3	16	14·0/57·2 (24·5)

*During four weeks before treatment with iron. †Immediately before treatment with iron was started. ‡During four weeks after treatment with iron was started. §After four weeks of treatment with iron.

concentrations <100 μg/l before treatment with erythropoietin.

Transferrin saturation is a good indicator of the current balance of supply and demand of plasma iron, although it is an inadequate indicator of the amount of iron stored.[2,3] In addition, Bainton and Finch showed that once the transferrin saturation falls below 16% iron supply for erythropoiesis may be inadequate.[4] Our data also suggest that, during treatment with erythropoietin, monitoring of transferrin saturation is more reliable for detecting functional iron deficiency than is monitoring of serum ferritin concentration.

We believe that functional iron deficiency will become an increasing problem as treatment with erythropoietin is used more widely unless prophylactic iron is given parenterally when indicated—that is, when transferrin saturation falls below 20%. This iron supplementation should also optimise the cost effectiveness of the drug.

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Randomised trial of two strategies offering women mobile screening for breast cancer

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High compliance is an important prerequisite for effective population screening.[1] Responses to breast cancer screening of 85% and over have been achieved in Sweden[2] and The Netherlands,[3] but in the United Kingdom responses have been more modest: 60% in Guildford and 72% in Edinburgh.[4] These responses resulted from active invitation to participate, though the precise methods used have not been reported.

We determined whether compliance would improve if a letter of invitation contained a definite appointment for screening rather than an open ended request to make an appointment.

Subjects, methods, and results

A sample of 450 women aged 45-64 was identified from the age-sex registers of two general practitioners from one practice in Aylesbury and randomly allocated to receive either a letter with an appointment (group 1) or an open ended letter of invitation (group 2) for breast cancer screening. The letters were signed by the general practitioner and had, as far as possible, identical texts. At the screening office alternate appointments were allocated to the two groups.

Women in group 1 were asked to contact the screening service to cancel or alter appointments but not to confirm them. Women in group 2 were invited to return a form indicating convenient times; an appointment was then sent. Non-responders were sent a reminder after three weeks. Non-attenders from both groups were sent another appointment.

Both groups were comparable for age, previous screening (56 (30%) and 69 (34%) respectively had been screened before as volunteers), and where they lived.

Three invitations were accidentally sent to men. These and women who had moved, were duplicated on the register, and were known to have been screened recently were excluded. Nine women were inadvertently sent invitations instead of appointments, and one was sent an appointment instead of an invitation; they were also excluded. This left 188 women in group 1 and 204 women in group 2.

The table gives the main results. Women in group 1 had a significantly higher rate of response than women in group 2. Significant differences remained when the 10 women inadvertently sent the wrong letter were included according to both the received and the intended strategies. Compliance was improved in group 1 after every contact, though individual differences were not significant, and was higher than that in group 2 for all age groups, for previously screened women, and for previously unscreened women ($p<0.05$).

Response to invitation to breast cancer screening by appointment (group 1) or open ended invitation (group 2). Figures are numbers (percentages) unless stated otherwise

	Group 1 (n=188)	Group 2 (n=204)
Mean age (years)	55·4	56·1
Screened at:		
First contact	131 (69·7)	131 (64·2)
Second contact	26* (13·8)	19† (9·3)
All other contacts	5‡ (2·7)	4§ (2·0)
Total	162‖ (86·2)	154 (75·5)

*After cancellation (13) or non-attendance (13).
†After reminder.
‡After both cancellation and non-attendance.
§After cancellation (2) or non-attendance (2).
‖Continuity adjusted $\chi^2=6·47$; df=1; p=0·01.

From a total of 273 appointments issued to women in group 1, 45 (24%) were unused through non-attendance; 32 (17%) became available for reuse—15 (80%) after cancellation and 17 (90%) after refusal or when letters were returned unopened. Unfilled and cancelled appointments in group 2 each accounted for under 2% (4) of the total.

Comment

This study shows that including an appointment in the invitation significantly enhances compliance with screening compared with an open ended invitation, confirming earlier findings reported for cervical screening.[5] The improvement persisted across all contacts and age bands and remained regardless of screening history. This improvement may have arisen because a definite appointment may place more onus on women to attend.

The postage for group 1 cost about half that for group 2. Also, clerical staff reported that they found the appointment strategy more straightforward than the invitation strategy, though the work entailed was different. Non-responders are never given appointments with a system of open ended invitations. With pre-allocated appointments several remain vacant unless overbooking is allowed. Overbooking of pre-allocated appointments, however, remains to be tried,