Drug Treatment of Disease

IRON PREPARATIONS FOR ANAEMIA

BY

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More than twenty years ago ferrous sulphate became established as a highly satisfactory and economical preparation for the treatment of iron-deficiency anaemia. Studies such as those of Witts (1936) and Davidson and Fullerton (1938) showed it to be at least as effective as any of the other iron compounds available at that time, including ferrous lactate, ferrous chloride, ferrous carbonate, iron and ammonium citrate, and colloidal iron, while it was cheaper and more convenient to dispense than any other compound.

In more recent years, however, a series of organic iron preparations such as ferrous gluconate, succinate, and fumarate and a range of chelated iron compounds have been introduced, to the accompaniment of extensive advertising campaigns, as supposedly more effective and less toxic alternatives to ferrous sulphate. In the first part of this article I propose to examine how these claims have survived the clinical trials designed to confirm or refute them. I shall then deal briefly with the question of comparative costs of oral preparations, and finally describe the compounds available for parenteral use.

EFFICACY AND TOXICITY

O'Sullivan *et al.* (1955) carried out one of the first reliable trials on the comparative value of ferrous sulphate, gluconate, and succinate. Tablets were given in doses arranged to provide equal amounts of elemental iron, 210 mg. daily, to groups of comparable patients, and the response was assessed with regard to rise of haemoglobin and the incidence of side-effects. There was little difference in efficacy between the three compounds, each producing an average daily haemoglobin rise between 1.1 and 1.25%. Gastro-intestinal symptoms of intolerance occurred in 3 out of 23 patients taking ferrous sulphate, in 1 out of 25 taking ferrous gluconate, and in 1 out of 25 taking ferrous succinate.

A survey of many papers dealing with the incidence of gastro-intestinal intolerance including nausea, vomiting, constipation, or diarrhoea during oral iron therapy strongly suggests that intolerance results chiefly from giving unnecessarily high doses, irrespective of the compound employed, or from psychological factors.

So far as dosage is concerned, quantities of elemental iron in excess of 300 mg. daily appear to have been given in most series of cases in which the figures for intolerance were high, and such high doses are certainly not necessary. Brumfitt (1959) found satisfactory and similar responses to either ferrous sulphate or ferrous gluconate in daily doses containing 149 mg. of elemental iron, roughly equivalent to two standard pills of ferrous sulphate or four of ferrous gluconate. None of the 30 patients included in this comparative trial developed symptoms of intolerance to either drug, and there was no intolerance among a further 50 patients treated with ferrous sulphate in similar dosage.

Psychological Intolerance

The psychological aspects of intolerance were first emphasized by Girdwood (1952). He found that 14 out of 16 patients who had developed gastro-intestinal symptoms while taking green ferrous sulphate tablets no longer did so when the same quantity of ferrous sulphate was taken in white pills. The possibility that suggestible subjects might tend to develop symptoms of intolerance when taking the familiar green ferrous sulphate tablets commonly issued at antenatal clinics, because they think side-effects are likely to occur rather than because the iron compound genuinely induces them, gains further support from figures of the incidence of intolerance in pregnant women given pills of differing appearance. Intolerance rates between 15 and 60% have commonly been encountered in pregnant women given standard green tablets in a dosage of 200 to 360 mg. of elemental iron daily, the higher rates of intolerance generally being associated with higher levels of dosage (Benstead and Theobald, 1952; Gatenby and Lillie, 1955; Talaga, 1955), whereas Edgar and Rice (1956) found intolerance in less than 5% of a large number of patients taking ferrous sulphate made up in white tablets with a daily intake of 200 mg. of iron.

A careful study of gastro-intestinal intolerance to oral iron compounds was made by Kerr and Davidson (1958a). They administered ferrous sulphate, ferrous gluconate, ferrous succinate, and ferrous calcium citrate in daily doses containing 105 mg. of elemental iron, and "known" and "unknown" control pills containing lactose to 93 healthy young women in a trial conducted so far as possible on the "double-blind" principle—that is, neither patient nor doctor was aware which of the preparations had been given to any individual, except in the case of the "known" control pills. None of the four iron compounds was found to induce toxic effects more frequently than did the "unknown" control pills containing lactose; for all these preparations the incidence of gastro-intestinal symptoms was between 15 and 20%. The "known" control pills produced virtually no toxic effects. The authors concluded that intolerance to these iron compounds, in the dosage given, was mainly psychological in origin.

Chelated Compounds

Fewer comparative trials have been conducted with the more recently introduced chelated iron compounds. These compounds are generally ring structures in which metallic iron is bound in a stable manner in an organic molecule. Herridge (1958) treated 10 patients with a form of "sytron" elixir, containing the ferric sodium salt of ethylenediamine tetra-acetic acid, and compared the response of their iron-deficiency anaemia with that of a further 20 patients treated with ferrous gluconate or succinate. Those receiving the chelate showed a significantly greater rise of haemoglobin, but the dosage of chelate in terms of elemental iron was between two

and three times that of the other salts. Perhaps for the same reason gastro-intestinal intolerance was greater in the patients taking chelate. Jennison (1958) found ferrous aminoacetosulphate ("plesmet") more effective and less toxic than ferrous gluconate when given to pregnant women with iron deficiency, but studies with other chelates (Seeberg *et al.*, 1954; Will and Vilter, 1954; Franklin *et al.*, 1958) appear to show that this type of compound is in general no better absorbed or tolerated than similar doses of ferrous sulphate. There therefore seems to be no great advantage to be gained from the use of chelates in the treatment of most patients with iron deficiency.

Post-gastrectomy Anaemias

In iron-deficiency anaemia following partial gastrectomy, on the other hand, there is some tentative evidence that iron chelates may have a special therapeutic place, since Hobbs and Discombe (1959) found a constant and rapid response to ferrous glycine sulphate, a chelated form of iron, whereas the response to ferrous sulphate proved erratic and unsatisfactory.

We may conclude from these studies that when minimal effective doses of ferrous sulphate are used—namely, 2 to 3 standard tablets daily, equivalent to 120 to 180 mg. elemental iron—the risk of intolerance is small. It can be further reduced by carefully avoiding any suggestion that gastro-intestinal disturbance may develop. Organic compounds such as ferrous gluconate and succinate, the equally effective ferrous fumarate, and the various chelated compounds appear to have no significant advantage over ferrous sulphate in terms of efficiency of action or incidence of side-effects when ferrous sulphate is given in the manner described. This statement applies to the great majority of cases of iron-deficiency anaemia, though it remains possible that organic salts or chelates may have a special advantage in the treatment of certain post-gastrectomy anaemias.

Dangers to Children

All oral iron compounds should be kept well out of the way of children, since they may readily be mistaken for sweets and consumed in large quantities. Relatively small overdoses of these compounds, and especially ferrous sulphate, may be highly dangerous to children.

COMPARATIVE COSTS

Since all the forms of iron hitherto discussed appear generally comparable in therapeutic efficiency and in toxicity when given in equivalent dosage with regard to content of elemental iron, their relative costs should clearly influence prescribing. Davidson and Richmond (1958) have examined this problem in detail, using figures from official sources and dealing with prescriptions dispensed throughout Scotland during May, 1957. They found that between 3 and 3½ million iron tablets were being dispensed each month in family practice, some 23% of them being ferrous sulphate, 50% ferrous gluconate, and 27% ferrous succinate. In hospitals about 10 million tablets were dispensed annually, about 46% being ferrous sulphate, 46% ferrous gluconate, and 8% ferrous succinate.

Now the cost of organic iron salts is much higher than that of ferrous sulphate, varying from five to 10 times the price for an equivalent iron content in the commonly used preparations and being considerably higher, sometimes very much higher, for chelated compounds and preparations with added vitamins. If

ferrous sulphate were always preferentially prescribed, Davidson and Richmond calculated that there would be a saving of about £40,000 per annum in Scotland alone. The pattern of prescribing may differ in England and Wales from that in Scotland, but if it is roughly the same the comparable saving to be achieved by the use of ferrous sulphate would be about £360,000 per annum. Moreover, since ferrous sulphate is customarily given in unnecessarily large doses, the use of minimal effective doses would further reduce the drug bill.

Vitamins

There is no real justification for giving iron preparations with added vitamins in the treatment of uncomplicated iron deficiency. The only vitamin known to facilitate absorption of iron is ascorbic acid, but with therapeutic doses of iron the addition of ascorbic acid does not appear to increase the efficiency of action and may reasonably be regarded as a needless expense (Kerr and Davidson, 1958b). Vitamins of the B group, added to several proprietary iron preparations, play no part in iron absorption, but greatly increase the cost.

PARENTERAL IRON

Two preparations have come into general clinical use for the parenteral administration of iron to patients who are undoubtedly intolerant of oral compounds, fail to absorb iron given by mouth, need rapid reconstitution of iron reserves, or have some gastro-intestinal disease liable to exacerbation if iron is given orally.

The first, saccharated iron oxide, is given intravenously, usually in doses of 5 ml., containing 100 mg. of iron, to a total calculated from the degree of anaemia, but commonly ranging from 1,000 mg. to 3,500 mg. in an adult. Care must be taken to give a clean intravenous injection, since the material is very irritant if deposited in the subcutaneous tissues. Reactions have proved a troublesome complication, though something can be done to reduce their incidence by the use of a small trial dose (25 mg.) before the course is undertaken, patients showing any sign of reaction to the initial dose being treated by some other means.

The chief features of the reactions to intravenous iron include cardiovascular symptoms, with fall of blood-pressure, tachycardia, and sometimes loss of consciousness, dyspnoea, cyanosis, vomiting, diarrhoea, and abdominal pain, and high pyrexia with rigors. They are of rapid onset, usually starting during the injection or within half an hour of its completion. Ross (1957) reported the incidence of toxic reaction in 802 anaemic patients treated with a standard preparation of intravenous saccharated iron oxide—"ferrivenin." With 100-mg. doses the overall incidence was 7.5%, and with 500-mg. doses the incidence rose sharply to 43%. Even with careful selection of patients, excluding those with chronic heart or lung disease who seem especially liable to respiratory reactions, and the use of no more than 100-mg. doses, the incidence of reactions is likely to remain about 5%.

The second iron compound for parenteral administration is an iron-dextran complex, "imferon," given by intramuscular injection. While it has been shown to be relatively free from immediate toxic effects, recent animal experiments have demonstrated a marked carcinogenic hazard of iron-dextran in rats and mice (Richmond, 1959; Haddow and Horning, 1960). I am not aware of any reports of local tumour formation

after imferon injections in man, despite very extensive use over the past five years, and it may be that the hazard does not apply to all species. Nevertheless, until the risks to man have been elucidated it would seem wise to discontinue the use of iron-dextran in medical practice (*Brit. med. J.*, 1960).

CONCLUSIONS

Ferrous sulphate in relatively small doses (2 to 3 tablets of 0.2 g. daily, providing 120 to 180 mg. elemental iron) is the most economical form of oral iron for general use. It is not significantly inferior to more expensive organic salts and chelates with regard to efficacy or gastro-intestinal toxicity when given in the proper dosage, and it is much cheaper.

Alternative oral preparations may reasonably be tried in the small proportion of patients who develop intolerance even to small doses of ferrous sulphate, though such patients may often react similarly to other compounds. For these intolerant patients, and for some others who fail to respond to oral iron or for other reasons require parenteral administration, intravenous saccharated iron oxide may be given, a careful watch being maintained for sensitivity reactions. Parenteral compounds are, of course, much more expensive than equivalent doses of oral iron, but in practice the high utilization of the iron reduces the difference in cost, and, since iron should not be given parenterally in preference to orally unless a specific indication exists, economic considerations are not of importance here.

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The booklet, *Home Guide for the Diabetic: Diet Instruction, Recipes and Other Guidance* (Iliffe and Sons, Ltd., Dorset House, Stamford Street, London, S.E.1, price 3s., by post 3s. 3d.), is based on the handbook issued to patients of the Leicester Royal Infirmary Diabetic Clinic. General guidance is given on such subjects as the method of giving insulin injections, hygiene for the diabetic, social-service arrangements, and general principles of nutrition. There are further sections on alternative food values, a special list of foods with low caloric value, recipes, weight-reducing diets, and a list of proprietary names of medical supplies.

MEDICAL RESPONSIBILITY IN ADOPTION

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The number of official adoptions in England and Wales is about 13,000 a year. Most of these entail a medical examination for purposes dissimilar in several respects from other types of medical examination. With the coming into force of a new Adoption Act it seems timely to consider what part the doctor plays in ensuring that adoption is practised wisely and with due regard to the well-being of the adopted children and society.

A doctor may be asked to examine and report on the health of a child proposed for adoption, or of the persons who propose to adopt. The request to do so will come from either the would-be adopters, the adoption agency (local authority or registered adoption society), or the mother who wishes her child to be accepted by an adoption agency for adoption.

The point at which the doctor will be approached is as soon as the question of getting a particular child adopted has been mooted, or when particular applicants have decided that they wish to adopt a particular child. He will be approached to examine the prospective adopters (a) when they make a general application to an adoption agency without specifying a particular child, or (b) when adopters are about to apply to a court for permission to adopt a particular child.

The doctor's report on the health of the infant has to be detailed and comprehensive, as required by the Regulations. His report on the health of the would-be adopters for the court will be summary; to meet the minimal requirements of the Act he need only state that the applicant whom he has examined "is physically, mentally, and emotionally suitable to adopt a child." Most of the adoption agencies, however, will ask for much more than this, and their forms are correspondingly more detailed—rather on the lines of a health insurance report. They pay particular attention to the applicants' emotional stability and medical reasons for not having children of their own instead of adopting. Medical reports on adopters are not required, however, when the child's natural parent (usually the mother of an illegitimate child) wishes to adopt him or when he is past compulsory school age.

As some of these requirements, especially those regarding a medical examination of the adopters, are new since the passing of the Adoption Act, 1958, it is likely that difficult questions of procedure and clinical appraisal will occasionally arise for doctors asked to assist in an adoption.

Reports on Infants

The examining doctor is not asked to give his opinion that the child is or is not suitable for adoption when he fills up the certificate for the court hearing; he is asked only to say, first, that he has informed the would-be adopters of his findings on mental and physical examination, and, secondly, that the child is or is not