

GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS

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It was the opinion of Thomas Sydenham that "iron may be given in the largest doses without inconvenience". His optimistic view has been shared in later generations by the originators of a large number of oral iron preparations which now compete for favour in the advertisement columns of the medical press. There is, however, a widespread belief among patients that iron inevitably causes gastrointestinal disturbance, particularly constipation.

To most patients ten years ago "iron" was synonymous with green ferrous-sulphate tablets. This preparation's popularity with the medical profession was well deserved. In correcting iron-deficiency anæmia it had been found at least as effective as any of the other available preparations (ferrous chloride, ferrous carbonate, iron and ammonium citrate, colloidal iron) and it had a considerable advantage in cost and convenience (Davidson and Fullerton 1938). During the past ten years a number of organic iron preparations have appeared on the market, and have been widely used. It is therefore desirable to re-examine the question of which oral preparation of iron is the most suitable for the treatment of anæmia, in both pregnant and non-pregnant patients.

O'Sullivan et al. (1955) compared three of the most popular preparations—ferrous sulphate, ferrous gluconate, and ferrous succinate. They gave the three compounds, in doses containing equal amounts of elemental iron (210 mg. daily) to matched groups of patients, and found similar rises in hæmoglobin level. Few other comparisons between iron compounds have been made with the same control of dosage and type of patient, but numerous papers attest the therapeutic effectiveness of most of the popular iron pills. Ferrous sulphate (Benstead and Theobald 1952, Devoe and Moses 1954, Talaga 1955, Gatenby and Lillie 1955, O'Sullivan et al. 1955), ferrous gluconate (Jasinski 1949, Haler 1952, Gatenby and Lillie 1955, O'Sullivan et al. 1955), ferrous succinate (O'Sullivan et al. 1955, Gillhespy 1955, Cope et al. 1956, Storm Mathiesen and Petersen 1956), ferrous calcium citrate (Talaga 1955), and several other compounds (Davidson and Fullerton 1938) have been shown to be capable of correcting iron-deficiency anæmia. In most of the papers cited, a rise in hæmoglobin level of more than 1% per day was obtained when the pills were taken conscientiously in the recommended dosage. Since the published evidence does not show that any one of these compounds is more efficient than the others, the choice between them depends mainly on two factors—cost and incidence of side-effects.

With regard to cost we are satisfied that ferrous sulphate is the least expensive preparation of iron available. (Davidson and Richmond 1958.) With regard to side-effects, experiments on animals have shown that in *very large* doses ferrous sulphate is appreciably more toxic than comparable amounts of iron and ammonium citrate, and two to five times as toxic as ferrous gluconate (Hoppe et al 1955, Brown and Gray 1955). Accidental poisoning with ferrous sulphate, usually in children, has sometimes been fatal (Reissman et al. 1955). It does not appear,

however, that the symptoms of which patients complain when taking therapeutic doses of iron are simply milder forms of those caused by acute poisoning, since the latter are partly due to excessive absorption of iron (Reissman and Coleman 1955). For instance, constipation is the most common complaint of patients taking iron, whereas diarrhoea is an almost constant feature of ferrous-sulphate poisoning.

Published reports of the incidence and severity of gastrointestinal intolerance to therapeutic doses of iron vary greatly.

This variation is seen particularly with ferrous sulphate, whether given alone or with traces of other metals (molybdenum, cobalt, copper). Thus various authors have reported intolerance-rates ranging from 0 to 60%. Many of the reports are difficult to assess, because inadequate information on dosage, number and type of patient, and definition of intolerance is given. Some of the papers in which adequate data have been recorded are summarised in table I. If the cases given very large doses of ferrous sulphate (360 mg. of iron daily) are excluded, the incidence of intolerance in 367 patients receiving an average of 220 mg. of ferrous sulphate daily is 4%, a figure comparable to that shown in table I as occurring after the ingestion of 210 mg. of ferrous gluconate daily.

In this analysis we have not taken into account the report by Talaga (1955), because the intolerance-rate of 60% in his series of patients was conspicuously different from that reported in all other trials included in table I in which comparable doses of iron were given.

Study of the reports also shows that the iron content of the preparations of ferrous sulphate was usually larger than that of the other compounds; that the pills employed varied widely in colour, size, and type of coating; that the series of patients were not always comparable; and that the definition of "side-effects" varied from mild symptoms to a degree of intolerance necessitating cessation of treatment.

It may be assumed that the enthusiasm shown by a doctor recommending treatment, and the statements which he makes to patients about the likelihood of side-effects, will also vary. These factors can be eliminated only by arranging a trial in which pills with identical coating and the same iron content are given to matched groups of patients on the "double blind" principle—neither the patient nor the doctor knowing which preparation is being employed until after the results have been assessed.

During such a trial carried out on antenatal patients by Kerr and Davidson (1958) a comparison was made between ferrous sulphate, ferrous gluconate, and inert tablets. The incidence of gastrointestinal symptoms attributed by the patients to their pills was similar in the three groups. It was felt that pregnant women might be unsatisfactory subjects for a detailed study of this kind, because they often suffer from constipation and heartburn, and because they spend a considerable amount of time sitting in queues at antenatal clinics, discussing their symptoms. Accordingly a second double-blind trial was planned, using as subjects healthy non-pregnant young women. The results are reported here.

Plan of the Experiment

The purpose of the trial was explained to the nursing staff of the Royal Infirmary, Edinburgh, and 100 volunteers requested. Each volunteer was given six packets of pills and asked to take them, in the dosage prescribed on the packets, after meals, from Monday to Friday during six successive weeks. No pills were taken on Saturdays and Sundays, and at the end of each week a questionnaire was completed giving details of any symptoms experienced during the preceding week.

TABLE I—INCIDENCE OF GASTROINTESTINAL INTOLERANCE TO ORAL IRON PREPARATIONS REPORTED BY VARIOUS AUTHORS

Ferrous preparation	Dose (mg. iron daily)	Trace metals added	Indication for treatment	No. of patients	Intolerance-rate (%)	Author
Sulphate	200	Nil	Pregnancy	27	4	Devoe and Moses 1954
"	240	Nil	"	41	60	Talaga 1955
"	360	Nil	"	207	57	Gatenby and Lillie 1955
"	210	Nil	Hypochromic anæmia	25	13	O'Sullivan et al. 1955
"	360	Copper, manganese	Pregnancy	51	35	Benstead and Theobald 1952
"	180-240	Cobalt	"	58	0	Holly 1955
"	240	Molybdenum	"	75	1	Lund 1951
"	360	"	"	15	14	Benstead and Theobald 1952
"	360	"	"	91	44	Gatenby and Lillie 1955
"	240	"	"	24	0	Devoe and Moses 1954
"	240	"	"	18	6	Talaga 1955
" (white)	200	Nil	"	140	5	Edgar and Rice 1956
Gluconate	210	Nil	"	109	14	Gatenby and Lillie 1955
"	210	Nil	Hypochromic anæmia	25	4	O'Sullivan et al. 1955
Succinate	210	Nil	"	25	4	O'Sullivan et al. 1955
"	105	Nil	"	150	<1	Gillhespy 1955
"	105	Nil	Pregnancy	49	2	Cope et al. 1956
Calcium citrate	150	Nil	"	48	0	Talaga 1955

Six symptoms were mentioned specifically on the form—nausea, vomiting, heartburn, abdominal discomfort, constipation, and diarrhoea—and a space was left to record "any other symptoms". The volunteers were asked to describe only symptoms which they believed were due to the pills; they were not asked to grade their severity but merely to say whether they were severe enough to prevent their taking the full course of treatment prescribed for that particular pill. If they were obliged to stop taking one pill on account of symptoms, they were asked to continue with the others according to schedule. They were told that the first five packets contained iron pills of various types, some of which would change the colour of the stools while others would not. The sixth packet was marked "control pills" and it was explained that these were given to make sure that the coating used on the other pills was not itself a cause of symptoms.

The five "iron pills" contained: ferrous sulphate; ferrous gluconate; ferrous succinate; ferrous calcium citrate; and lactose. The last is hereafter referred to as the "unknown" control pill. The pills known to the patient as the "control" pills also contained lactose, and were identical in appearance and composition to the "unknown" control pills.

Careful consideration was given to the dosage of iron to be incorporated in the pills.

It was essential that the daily iron intake should be the same irrespective of which preparation was being taken. The usual dose of ferrous gluconate is one 300 mg. (gr. 5) pill and of ferrous succinate one 150 mg. (gr. 2½) pill, each containing 35 mg. of elemental iron, given three times a day, making a total of 105 mg. of iron daily. The dose of ferrous calcium citrate recommended by the manufacturers is two 300 mg. (gr. 5) pills each containing 25 mg. of elemental iron, given three times a day, making a total of 150 mg. of iron per day. Ferrous sulphate, however, is usually prescribed as one 180 mg. (gr. 3) pill containing 60 mg. of elemental iron, three times a day, making a total of 180 mg. of iron daily. At the outset a decision had to be made as to whether it was desirable to increase the dose of elemental iron in each ferrous gluconate and succinate pill to 60 mg.—i.e., about double the usual therapeutic dose—or to reduce the amount of elemental iron in each ferrous sulphate tablet from 60 mg. to 35 mg. The

latter choice was made because evidence had been obtained by Kerr and Davidson (1958) that ferrous sulphate was effective when given in the smaller dose.

Each ferrous-sulphate, gluconate, and succinate pill contained 35 mg. of iron; the dose of these and of the "known" and "unknown" control pills was one, three times a day. Ferrous calcium citrate could not be prepared in pills of the same size, with an iron content of 35 mg.; it was therefore made up in pills containing 17.5 mg. of iron, identical in other respects to the control pills, and given in a dose of two tablets three times a day. To this extent the ferrous calcium citrate pills were distinguishable from the others; but, with this exception, the comparison was carried out as a double blind experiment, the key being opened only after the results had been analysed. The pills were identical in size, shape, colour, and coating.

The volunteers were assigned at random to five groups which took the pills in different orders.

103 nurses volunteered. 7 failed to complete it for reasons unconnected with the pills (intercurrent illness, night duty, holidays). 3 others dropped out because they experienced unpleasant symptoms. One of these complained of abdominal pain and diarrhoea, and another of constipation, while taking ferrous sulphate. The third volunteer had various symptoms while taking ferrous calcium citrate, ferrous gluconate, and "unknown" control pills.

The 93 volunteers who completed the trial were all healthy young women aged 18-30 years (mean age 21). The haemoglobin level was not estimated routinely, but 23 volunteers when visiting the blood clinic to collect their pills asked that this estimation should be carried out. Their haemoglobin levels ranged from 11.7 to 15.5 g. per 100 ml. (79-105%), the mean being 13.9 g. (94%). This suggests that most of the subjects were not significantly anæmic. 11 had been treated with oral iron in the past, but none could recollect any untoward symptoms from this.

Results

The replies given by the 93 who completed the trial are summarised in table II.

In total incidence, "toxic effects" from the "unknown" control pills did not differ significantly from those accompanying any of the preparations containing iron, whether the slight or doubtful symptoms were

TABLE II—INCIDENCE OF ALL GASTROINTESTINAL SYMPTOMS IN 93 SUBJECTS WHO COMPLETED THE TRIAL

Iron preparation	1 No symptoms	2 Slight or doubtful symptoms	3 Symptoms +	4 Symptoms ++	5 Total with significant symptoms (3+4)	6 Total with no significant symptoms (1-2)
Ferrous sulphate	58	12	22	1	23	70
" gluconate	69	4	17	3	20	73
" succinate	59	13	19	2	21	72
" calcium citrate	63	11	14	5	19	74
"Unknown" control	65	8	18	2	20	73
"Known" control	91	0	2	0	2	91

+ = symptoms definite but treatment continued.

++ = symptoms severe enough to stop treatment with that pill.

TABLE III.—INCIDENCE OF SYMPTOMS ATTRIBUTED TO IRON PILLS (Group A: 20 subjects who complained of symptoms with "unknown" control pills. Group B: 73 subjects who did not complain)

Iron preparation	Total no.	No. with definite symptoms	Intolerance rate (%)
<i>Group A:</i>			
Ferrous sulphate	20	10	50
" gluconate	20	8	40
" succinate	20	5	25
" calcium citrate	20	7	35
<i>Group B:</i>			
Ferrous sulphate	73	13	18
" gluconate	73	12	16
" succinate	73	16	22
" calcium citrate	73	12	16

included in the analysis or not ($P > 0.05$). Only 2 volunteers recorded symptoms while taking the "known" control pills; 1 complained of heartburn and 1 of constipation. When the incidence of side-effects was calculated for the whole group of 103 (using the incomplete replies of the 10 nurses who failed to complete the trial) there was again no significant difference between iron preparations and "unknown" control pills.

It was clear that factors other than iron were responsible for most of the "toxicity" reported by these volunteers. One possibility was that a proportion of them were unusually suggestible, and developed symptoms whenever they took pills which they believed to contain iron. If this were so, it would be important to exclude such subjects from consideration when comparing the iron preparations.

To test this hypothesis the 93 who completed the trial were divided into two groups—the 20 nurses who complained of symptoms with "unknown" control pills (group A), and the 73 who did not (group B). Table III shows that there was more intolerance to iron-containing pills in group A than in group B, and in the case of ferrous sulphate and ferrous gluconate this difference was significant ($P < 0.05$). In group B the intolerance-rates to the four iron preparations did not differ significantly from one another.

Analysis of the individual symptoms reported with the various iron pills shows that no characteristic symptom complex resulted from taking any of the pills. With each preparation, constipation and abdominal discomfort were the commonest symptoms; the incidence of all the others was less than 10%.

11 of the subjects who did not complain of symptoms with control pills had symptoms with more than one of those containing iron. 3 of them reported constipation with each of two preparations; but otherwise there was no consistency in the symptoms of which any individual complained. Nobody reported symptoms with all four iron preparations. There was therefore no evidence of the occurrence of true iron intolerance embracing all forms of oral iron.

Discussion

The importance of psychological factors in producing both beneficial and undesirable results from drug therapy is now widely recognised.

Girdwood (1952) focused attention on this aspect of iron intolerance. In a clinical trial of molybdenised ferrous sulphate he found that many patients who were intolerant of ferrous sulphate had no symptoms when taking the preparation containing trace amounts of molybdenum. Realising that this might be partly due to the difference in appearance between the pills, he administered ferrous sulphate, in the form of white pills, to 16 patients who had previously developed

gastrointestinal symptoms when taking exactly the same preparation in the form of green pills ('Fersolate'). 14 of the 16 took white ferrous-sulphate pills without complaint.

Edgar and Rice (1956) used similar white ferrous-sulphate pills in the prophylaxis of anæmia of pregnancy, and found a much lower intolerance-rate than most other investigators using the green pills.

Two main factors contribute to this finding.

Firstly, mild gastrointestinal disturbances, particularly constipation, are common in any group of young women, and particularly in the pregnant women, who in Great Britain form the majority of the patients receiving iron therapy. There is a strong tendency for the patient to attribute these symptoms to any medicine she is taking, especially if she knows that it may have such effects. This tendency may have been accentuated in the present trial since the volunteers were specifically asked to note any gastrointestinal disturbance, and their attention was directed to likely symptoms by the questionnaire. That transient incidental symptoms were responsible for many of the "toxic effects" reported is suggested by the observation that more than half the nurses who complained of symptoms with "unknown" control pills had no symptoms when taking one or other of the iron preparations.

Secondly, suggestible people can develop symptoms of psychological origin, not previously present, when taking pills which they believe will upset them.

This phenomenon is observed in most clinical trials, and the proportion of subjects who exhibit it may be surprisingly high. In a trial of phenoxybenzamine for the treatment of chilblains (College of General Practitioners 1957) 13% of the patients taking placebo pills complained of dizziness or other symptoms which they had been warned might occur with phenoxybenzamine. In a similar long-term trial of tetracycline (Moyes and Kershaw 1957) 39% of those receiving placebos complained of diarrhoea.

In the present investigation the incidence of symptoms in the group as a whole was almost the same, whether the iron was taken as ferrous sulphate, ferrous gluconate, ferrous succinate or ferrous calcium citrate. Similar "toxic effects", however, were reported equally often after taking the "unknown" control pills which were thought to contain iron but in fact contained only lactose. It is of great interest that with the "known" control pills (identical in every way with the "unknown") only 2 subjects reported symptoms. This observation may be interpreted in two ways: either (1) most of the subjects experienced no symptoms while taking the "known" control pills, or (2) the symptoms arose, but, because they could not be ascribed to the pills, were ignored or attributed to other factors.

Our impression that the "toxic effects" of the pills were not due to iron is strengthened by our finding that no symptom or group of symptoms was constantly associated with any particular preparation of iron and that, when they were on iron therapy, none of the subjects consistently complained of symptoms distinguishable from those they reported when "unknown" inert pills were taken.

It should be emphasised that the conditions in this trial were not identical with those in clinical practice.

Firstly, the dose of iron chosen for the trial approximated closely to that used in practice when commercial preparations of ferrous gluconate and ferrous succinate are prescribed, but was about half that usually employed when ferrous sulphate is prescribed. Secondly, the pills were given for only five days at a time. (This period was thought long enough for symptoms

due to gastrointestinal irritation to appear.) Thirdly, this trial differed from previous therapeutic trials in that the people taking part in it were neither anaemic nor pregnant. We would, however, point out that we obtained almost identical results in a similar trial on pregnant women (Kerr and Davidson 1958).

We conclude that a large proportion of the symptoms experienced during therapy with oral iron preparations is psychological in origin. The possibility that some patients have true iron intolerance cannot be excluded; but the incidence of toxicity—at least with doses of 35 mg. of iron three times a day—must be very low. Among those whose complaints were confined to iron preparations, the symptom most commonly reported was constipation. Other gastrointestinal effects were variable, and usually mild, and they were never reported by more than 12% of subjects.

It will take a long time to dispel the popular belief that iron pills inevitably cause unpleasant side-effects, but reassurance and enthusiastic propaganda could do a great deal to reduce the "intolerance rate". Recently we have found it well worth while to explain to patients that the pills they are about to take have been tested in a blind trial and found to cause no more symptoms than pills containing sugar.

Summary

1. Ferrous sulphate, ferrous gluconate, ferrous succinate, ferrous calcium citrate, and "known" and "unknown" control pills (containing lactose) were administered to 93 healthy young women in a double-blind trial. The incidence of gastrointestinal symptoms attributed to the pills was assessed from the replies to a questionnaire.

2. Virtually no toxic effects were reported from "known" control pills containing lactose, but the exactly similar "unknown" control pills, which were thought by the subjects to contain iron, produced as many side-effects as the pills which did in fact contain it.

3. None of the four iron compounds was found to be significantly more "toxic" than inert pills containing lactose. Hence it was concluded that intolerance to these iron preparations, in the dosage given, was mainly psychological in origin.

We wish to express our thanks to the nurses who took part in the trial and to Miss Law, assistant lady superintendent, Royal Infirmary, Edinburgh, who helped to recruit the volunteers; to Dr. Gordon Fryers, of John Wyeth and Brother, Ltd. for the supply of ferrous sulphate, ferrous gluconate, and control pills; to Mr. John Williams, of Calmic Ltd. for the supply of ferrous succinate; and to Mr. Reginald George, of Ortho Pharmaceuticals Ltd. for the supply of ferrous calcium citrate, used in the trial.

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ACCIDENTAL HYPOTHERMIA A COMMON CONDITION WITH A PATHOGNOMONIC ELECTROCARDIOGRAM

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INDUCED hypothermia now plays an accepted part in surgery of the heart and brain and has therefore been studied a great deal by physiologists (Kayser 1957). Clinicians, however, have paid comparatively little attention to accidental hypothermia, and Rees (1958), who recently reported four cases, has stated that in clinical medicine it is uncommon.

The electrocardiogram in preoperative hypothermia has features characteristic enough to be pathognomonic (Emslie-Smith 1956, Fleming and Muir 1957). As temperature falls, the heart-rate slows and the intervals PR, QRS, and QTC all lengthen. A conspicuous extra deflection appears at the junction of the QRS complex and the ST segment. This "junction deflection" (J deflection) is slowly inscribed and is usually most obvious in lead V₄, where it is directed upward. In other leads the base of the QRS complex is widened. In the vectorcardiogram these features are represented by an extra loop between the QRS and T loops (Emslie-Smith 1958). When the J deflection is large, the T wave may become inverted.

Tomaszewski (1938) published the electrocardiogram of a vagrant dying from cold. Since then the electrocardiogram in accidental hypothermia seems to have been recorded on eight occasions only (Wayburn 1947, Graybiel and Dawe 1948, Laufman 1951, Karnell et al. 1955, Björck and Johansson 1955, Rees 1958). Only a few of these records showed the characteristic J deflection, and Rees (1958) did not see it in the electrocardiograms of his patients.

I have recently encountered eight cases of accidental hypothermia, and heard of another, in circumstances which suggest that the condition is very much commoner than is supposed. In seven cases adequate electrocardiograms showed the pathognomonic pattern; in the eighth it was obscured by bundle-branch block.

Case-reports

Case 1.—A mentally depressed woman, aged 50, was found unconscious. It was thought that she had swallowed a large dose of carbromal and barbiturate. She was cyanosed and deeply comatose, with shallow respirations occurring only three times a minute. All her tendon-reflexes were absent, her systolic blood-pressure was 60 mm. Hg, and her rectal temperature was 30.2°C (86°F).

An endotracheal tube was passed, and oxygen was given by artificial respiration with a closed circuit. An intravenous infusion of plasma was started. The electrocardiogram then showed sinus bradycardia (rate 47 a minute). Changes typical of hypothermia were present: PR measured 0.16 sec., QRS 0.08 sec., and QTC 0.57 sec.; a small, slowly inscribed, extra deflection was present between QRS and the early part of the ST segment (J deflection); it was directed upward in leads I, II, III, aVL, aVF, V₄, and V₆, and downward in lead aVR.

The patient died after 48 hours' coma.

Case 2.—A grossly myxoedematous woman, aged 75, was found naked and unconscious. Her heart sounds were faint, blood-pressure 150/90 mm. Hg, and respirations 20 a minute. There were no focal neurological signs. Her rectal temperature was 27°C (80.6°F). The electrocardiogram showed sinus rhythm (rate 30 a minute). It was characteristic of hypothermia: PR measured 0.19 sec., QRS 0.11 sec., and QTC 0.58 sec.; in leads aVL, V₄ and V₅ a small J deflection was present between