

ABSORPTION FROM DIFFERENT TYPES OF IRON TABLETS -
CORRELATION BETWEEN SERUM IRON INCREASE AND TOTAL ABSORPTION OF IRON

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ABSTRACT

The absorption of iron from three different iron tablets - rapidly-disintegrating ferrous sulphate and ferrous carbonate tablets and slow-release ferrous sulphate tablets - was studied in healthy subjects with a serum iron technique and by whole-body counter measurements. A solution of ferrous sulphate was used as a reference. There were no differences in the absorption from the ferrous sulphate preparations, but the ferrous carbonate tablets were less well absorbed. Good correlation was found between the maximal serum iron response and the total absorption of iron and it was concluded that serum iron studies may be used for semiquantitative measurements of iron absorption in comparative studies on different iron preparations.

INTRODUCTION

In a previous study it was shown that the increase of serum iron after an oral dose of iron could be used as a semiquantitative measure of iron absorption (Ekenved et al 1976). The study was performed with ferrous sulphate in solution. In the present investigation the method was tested in comparative absorption studies with different tablet preparations. The studies were performed in healthy male subjects and the following three tablets were tested: rapidly-disintegrating ferrous sulphate and ferrous carbonate tablets and slow-release ferrous sulphate tablets. The relationship between the serum iron response and the total absorption of iron was studied by following the serum iron concentration for 6-8 hours and measuring the total absorption of iron in a whole-body counter.

MATERIAL AND METHODS

The studies were performed in 30 healthy, male volunteers aged 20-41 years (mean 25 years). The average weight was 71 kg (range 60-90 kg). All had a haemoglobin value within the normal range (13-17 g/100 ml). One subject (No 29) had been a regular blood donor. None had had any significant blood loss during the previous six months.

The design of the absorption studies was the same as previously described (Ekenved et al 1976). The serum iron concentration was followed for 6-8 hours, and the total amount of blood drawn in each study varied between 120 and 160 ml. The whole-body counter measurements and the determinations of serum iron and TIBC were performed as previously described (Ekenved et al 1976).

Three different series of subjects were studied. In each a tablet preparation containing 100 mg ferrous iron was compared with a solution of ferrous sulphate containing the same amount of iron using a randomized, cross-over design. Ten subjects were included in each series and the following iron preparations were studied:

- 1) rapidly-disintegrating ferrous sulphate tablets (series I)
- 2) rapidly-disintegrating ferrous carbonate tablets (series II)
- 3) slow-release ferrous sulphate tablets (series III)

All tablets were given with 125 ml of water. The iron solutions were given in a total volume of 125 ml including rinsings. All iron solutions and tablets were labelled with ^{59}Fe . The individual total activity of ^{59}Fe retained was less than 3 μCi .

Test preparations

The solution of ferrous sulphate contained 100 mg of ferrous iron and was prepared by dissolving ferrous sulphate together with 100 mg ascorbic acid in tap water. The iron was labelled by adding a tracer dose of $^{59}\text{FeCl}_3$.

The rapidly-disintegrating ferrous sulphate tablets were prepared from ^{59}Fe -labelled $\text{FeSO}_4 \cdot 4\text{H}_2\text{O}$. The disintegration time in vitro by the USP XVIII method (United States Pharmacopeia 1970) was 5 minutes both in water and in simulated gastric juice. The dissolution of iron in vitro was completed within 10 minutes, when tested in water or simulated gastric juice (USP XVIII) at an agitation rate of 100 rpm using a beaker method previously described (Alpsten et al 1976).

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The slow-re soluble matrix were prepared fi was 44, 59, 79 hours, when test beaker method pr ponding values v and 94 per cent.

Radioiron labell

^{59}Fe -labelled procedure: FeSO_4 dissolved in wat thorough mixing, adding ethanol.

^{59}Fe -labelled $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and a in water. A trac obtained by prec was then incorpo (Höglund et al 1 carbonate.

Statistics

Standard stat: data between the matched-pairs sig

volunteers aged 20-30 kg (range 60-90 kg) (range 13-17 g/100 g body weight). None had had any iron supplements in the 6 months.

As previously reported, the concentration was followed in each study by radioisotope measurements and compared as previously.

In each study a tablet was compared with a solution of iron using a procedure included in each study. The results are summarized in series I, II and III. The results of the iron solutions are given in Table 1. All iron measurements are given as individual total iron.

100 mg of ferrous sulphate together with 100 mg of ascorbic acid was prepared by adding a

100 mg of ferrous sulphate tablets were compared. The disintegration time in vitro (Höglund 1970) was compared. The dissolution rate, when tested in simulated gastric juice at an agitation rate of 40 rpm (Alpsten et al

The rapidly-disintegrating ferrous carbonate tablets were prepared from ^{59}Fe -labelled ferrous carbonate which had been incorporated into a sugar mass to avoid oxidation (Höglund et al 1973). The disintegration time in vitro by the USP XVIII method was 10 minutes both in water and in simulated gastric juice. The dissolution of iron in vitro was completed within 15 minutes, when tested in simulated gastric juice by the same method as was used for the ferrous sulphate tablets. In water practically no iron dissolved within 30 minutes, but finely dispersed ferrous carbonate particles were suspended in the dissolution medium.

The slow-release ferrous sulphate tablets were of an insoluble matrix type (Duroferon® Durules®) (Sjögren 1971). The tablets were prepared from ^{59}Fe -labelled $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$. The dissolution of iron was 44, 59, 79 and 90 per cent, respectively, after 1, 2, 4 and 6 hours, when tested in water at an agitation rate of 40 rpm using a beaker method previously described (Alpsten et al 1976). The corresponding values when tested in simulated gastric juice were 45, 60, 82 and 94 per cent.

Radioiron labelling of the iron compounds

^{59}Fe -labelled ferrous sulphate was prepared using the following procedure: $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and ascorbic acid (5 mg per 100 mg Fe^{2+}) were dissolved in water. A tracer dose of $^{59}\text{FeCl}_3$ was added and after thorough mixing, ^{59}Fe -labelled $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ was made to precipitate by adding ethanol. The precipitate was then dried.

^{59}Fe -labelled ferrous carbonate was prepared in the following way: $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and ascorbic acid (5 mg per 100 mg Fe^{2+}) were dissolved in water. A tracer dose of $^{59}\text{FeCl}_3$ was mixed in. Labelled FeCO_3 was obtained by precipitation with a solution of NaHCO_3 . The precipitate was then incorporated into a sugar mass using a special technique (Höglund et al 1973), in order to prevent oxidation of the ferrous carbonate.

Statistics

Standard statistical methods were used. Differences in absorption data between the iron preparations were tested with the Wilcoxon matched-pairs signed-ranks test (Siegel 1956).

RESULTS

Series I. Rapidly-disintegrating ferrous sulphate tablets

On one occasion the tablet was dissolved and administered as a solution and on another occasion it was swallowed intact. One subject had to be excluded because of missing absorption data due to a technical failure in the whole-body counter set-up. The results for the remaining 9 subjects are given in Table I and Fig. 1.

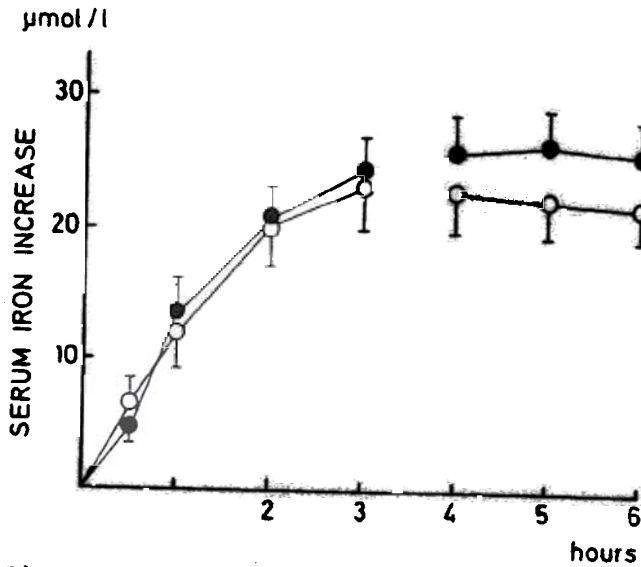


Fig. 1
Series I. Increase of serum iron after 100 mg of ferrous iron. Mean and SEM from 9 subjects.
O: solution of ferrous sulphate
●: rapidly-disintegrating ferrous sulphate tablets

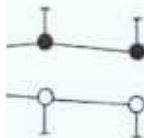
The mean absorption of iron was 8.9 ± 0.6 (Mean \pm SEM) per cent, when the tablet was given undissolved. The corresponding value when the tablet was dissolved before ingestion was 8.3 ± 0.7 per cent. The mean maximal increases of serum iron were 27.4 ± 2.6 and 24.3 ± 2.9 $\mu\text{mol/l}$, respectively. The differences in the absorption values and the maximal increases of serum iron were not statistically significant (N.S.). The serum iron curves were similar with the two preparations. The median time to reach the maximal serum iron concentration was 3 hours with the solution and 4 hours with the tablets (N.S.). There were no significant differences in serum iron concentrations between the tablet and the solution at any time during the study.

TABLE I
Series I. Iron absorption and maximal increase of serum iron after administration of 100 mg of iron as rapidly-disintegrating ferrous sulphate tablets to 9 healthy male subjects. The tablets were either dissolved and taken as a solution or were swallowed intact

Subject	Dissolved tablet		Intact tablet		TIBC $\mu\text{mol/l}$
	Before admi.	Iron ab-	Iron ab-	Max serum	

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the study.

TABLE I

Series I. Iron absorption and maximal increase of serum iron after administration of 100 mg of iron as rapidly-disintegrating ferrous sulphate tablets to 9 healthy male subjects. The tablets were either dissolved and taken as a solution or were swallowed intact

Subject	Dissolved tablet			Intact tablet			TIBC $\mu\text{mol/l}$
	Before admini- stration Serum iron $\mu\text{mol/l}$	Iron ab- sorption mg	Max. serum iron in- crease $\mu\text{mol/l}$	Before admini- stration Serum iron $\mu\text{mol/l}$	Iron ab- sorption mg	Max. serum iron in- crease $\mu\text{mol/l}$	
1	20.6	10.6	34.5	28.1	8.5	31.1	59.2
2	26.9	8.6	19.9	18.6	6.0	22.0	54.6
3	28.5	5.2	16.8	26.7	7.4	31.1	78.9
4	25.4	8.2	28.1	19.5	10.9	31.3	-
5	15.0	5.5	19.9	30.8	7.4	10.2	59.8
6	20.2	9.6	38.8	21.7	11.5	31.0	57.6
7	33.1	10.6	24.2	19.3	9.6	35.3	-
8	39.9	6.5	11.8	15.9	8.4	21.8	60.7
9	20.9	10.1	24.9	19.9	10.7	32.8	-
Mean	25.6	8.3	24.3	22.3	8.9	27.4	61.8
SEM	2.5	0.7	2.8	1.7	0.6	2.6	3.5
Wilcoxon matched-pairs signed-ranks test							
\longleftrightarrow N.S. \longleftrightarrow							

Series II. Rapidly-disintegrating ferrous carbonate tablets

Each subject received a rapidly-disintegrating ferrous carbonate tablet, which was swallowed whole, and a solution of ferrous sulphate. One subject (No 19) was not fasting when receiving the ferrous sulphate solution and the results for this subject were omitted when comparing the absorbability of iron from the two preparations. The results are given in Table II and Fig. 2.

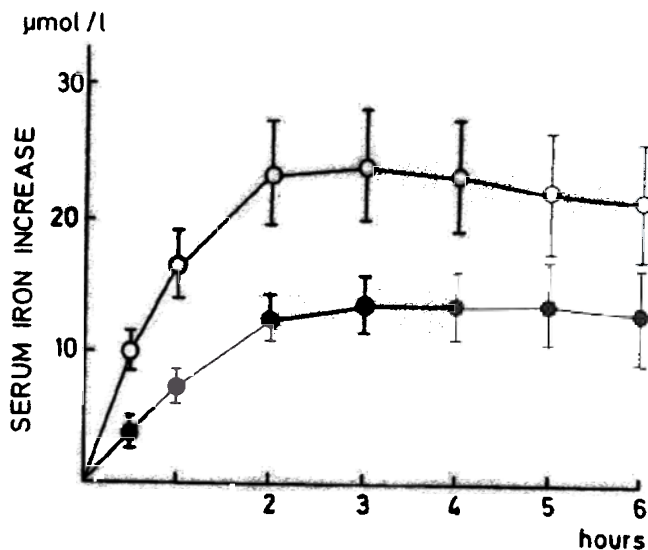


Fig. 2

Series II. Increase of serum iron after 100 mg of ferrous iron. Mean and SEM from 9 subjects.

○: solution of ferrous sulphate

●: rapidly-disintegrating ferrous carbonate tablets

The absorption of iron was higher from the ferrous sulphate solution than from the ferrous carbonate tablets in 7 out of 9 subjects. The mean values were 8.9 ± 1.1 and 5.2 ± 0.8 per cent, respectively. This difference was statistically significant ($p < 0.05$). The mean values for the maximal increases of serum iron were 25.3 ± 4.2 and 16.0 ± 3.2 $\mu\text{mol/l}$ after the two preparations (N.S.). Six out of 9 subjects showed the highest values after the ferrous sulphate solution. The median time until the maximal serum iron concentration was reached was the same (3 hours) for both preparations.

TABLE II

Series II. Iron absorption and maximal increase of serum iron after administration of 100 mg of iron as ferrous sulphate in solution and as rapidly-disintegrating ferrous carbonate tablets to 10 healthy male subjects

Subject	Ferrous sulphate solution		Ferrous carbonate tablets	
	Before administration Serum iron	Iron absorption mg	Before administration Serum iron	Max. serum iron in- $\mu\text{mol/l}$

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TABLE II

Series II. Iron absorption and maximal increase of serum iron after administration of 100 mg of iron as ferrous sulphate in solution and as rapidly-disintegrating ferrous carbonate tablets to 10 healthy male subjects

Subject	Ferrous sulphate solution			Ferrous carbonate tablets			TIBC μmol/l
	Before admi- nistration Serum iron μmol/l	Iron ab- sorption mg	Max. serum iron in- crease μmol/l	Before admi- nistration Serum iron μmol/l	Iron ab- sorption mg	Max. serum iron in- crease μmol/l	
10	16.1	10.5	37.2	11.8	8.3	21.5	74.1
11	16.1	6.6	10.6	10.6	7.6	8.4	65.7
12	23.3	5.4	19.2	51.7	6.7	21.1	78.4
13	27.6	6.8	16.6	21.8	4.7	10.6	51.0
14	41.2	7.9	17.5	25.4	3.4	21.8	59.8
15	14.1	12.0	46.7	9.5	2.6	4.1	70.5
16	19.9	9.4	30.8	18.4	8.1	34.7	55.3
17	15.4	5.9	14.0	13.2	2.6	9.8	57.1
18	23.6	15.4	35.3	24.5	3.1	11.6	56.4
19 ¹	7.2	0.7	3.6	13.4	5.8	19.5	60.5
Mean	21.9	8.9	25.3	20.8	5.2	16.0	63.1
SEM	2.8	1.1	4.2	4.4	0.8	3.2	3.2
Wilcoxon matched-pairs signed-ranks test	← P < 0.05			← N.S. →			

¹This subject had not fasted according to instructions before administration of the ferrous sulphate solution and is therefore excluded from the mean values.

Series III. Slow-release ferrous sulphate tablets

The subjects received on one occasion a slow-release ferrous sulphate tablet, which was swallowed whole, and on another occasion a solution of ferrous sulphate. The results are shown in Table III and Fig. 3.

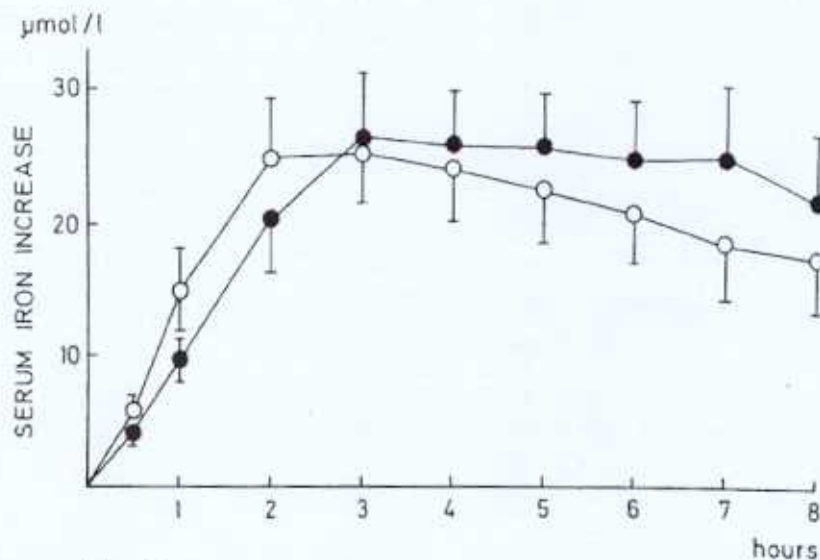


Fig. 3

Series III. Increase of serum iron after 100 mg of ferrous iron. Mean and SEM from 10 subjects.

O: solution of ferrous sulphate

●: slow-release ferrous sulphate tablets

The mean absorption of iron was 9.2 ± 2.1 per cent from the slow-release tablets and 8.9 ± 1.5 per cent from the solutions (N.S.). The mean maximal increase of serum iron was 27.7 ± 4.5 and 26.6 ± 4.3 $\mu\text{mol/l}$, respectively (N.S.). One subject (No 29), who was a blood donor, had a considerably higher absorption and serum iron increase than the other subjects. The serum iron curves were similar with the two preparations. The median time until the maximal serum iron concentration was reached was 3.5 hours with the slow-release tablets and 3 hours with the solution (N.S.).

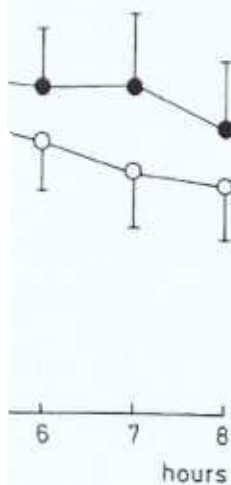
TABLE III

Series III. Iron absorption and maximal increase of serum iron after administration of 100 mg of iron as ferrous sulphate in solution and as slow-release tablets to 10 healthy subjects

Subject	Solution		Slow-release tablets		TIBC $\mu\text{mol/l}$
	Before administration	Iron absorption	Before administration	Iron absorption	
		Max. serum iron in-		Max. serum iron in-	

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TABLE III

Series III. Iron absorption and maximal increase of serum iron after administration of 100 mg of iron as ferrous sulphate in solution and as slow-release tablets to 10 healthy subjects

Subject	Solution		Slow-release tablets				TIBC µmol/l
	Before admi- nistration Serum iron µmol/l	Iron ab- sorption mg	Max. serum iron in- crease µmol/l	Before admi- nistration Serum iron µmol/l	Iron ab- sorption mg	Max. serum iron in- crease µmol/l	
20	19.3	7.0	20.0	23.3	6.5	27.0	63.4
21	19.7	10.2	28.3	22.6	5.6	12.7	63.5
22	23.4	7.5	19.7	27.4	5.4	15.0	60.0
23	20.4	4.6	20.8	25.4	5.9	27.2	59.1
24	21.3	6.2	25.2	18.4	5.1	25.2	62.1
25	23.3	7.1	20.4	23.6	6.6	13.8	60.0
26	7.7	7.6	15.8	13.8	12.6	42.6	65.7
27	28.1	7.9	33.1	27.0	10.3	30.1	67.3
28	36.5	9.5	20.0	27.6	7.1	24.2	63.2
29	16.1	21.4	62.8	18.4	27.0	59.4	75.2
Mean	21.6	8.9	26.6	22.8	9.2	27.7	63.9
SEM	2.4	1.5	4.3	1.4	2.1	4.5	1.5
Wilcoxon matched-pairs signed-ranks test							N.S.

DISCUSSION

The most exact determinations of iron absorption are performed by radioisotope techniques. However, sometimes non-radioactive methods are preferable. This is the case when performing comparative studies on different iron preparations. Labelling of radioactive iron tablets must be done before the manufacturing process and it may thus be difficult to obtain labelled tablets with the same disintegration and dissolution properties as the commercially available unlabelled tablets. Without such an equivalence radioisotope studies will not be very meaningful.

In an earlier study (Ekenved et al 1976) a good correlation was found between the total absorption of iron as measured in a whole-body counter and the maximal increase of serum iron after an orally administered solution of iron. However, the applicability of the serum iron method in comparative studies on tablets with different disintegration and dissolution properties has never been studied. This was done in the present investigation where two rapidly-disintegrating tablets containing iron salts with different dissolution properties - ferrous sulphate and ferrous carbonate - were studied. A slow-release preparation containing ferrous sulphate was also included in the study.

The in-vitro dissolution of iron from the rapidly-disintegrating ferrous sulphate tablets was rapid in both water and simulated gastric juice, whereas the dissolution of iron from the ferrous carbonate tablets was virtually nil in water but rapid in simulated gastric juice. The dissolution of iron from the slow-release tablets was the same in the two dissolution media - about 40 per cent after 1 hour and nearly 100 per cent after 6 hours. This dissolution rate was in agreement with that of the commercially available product (Duroferon® Durules®).

The absorption of iron, measured in a whole-body counter, from the rapidly-disintegrating ferrous sulphate tablets was the same as from a solution prepared from the same tablet. The absorption from the rapidly-disintegrating ferrous carbonate tablets was significantly lower than from the ferrous sulphate solution. The lower absorbability of iron from ferrous carbonate tablets is in accordance with the finding by Hallberg (1970) of a lower absorption of iron in blood donors from ferrous carbonate administered in a dose of 30 mg iron t.i.d. than from rapidly-disintegrating ferrous sulphate tablets in the same dosage. Höglund et al (1973) did not find any significant differences

in the absorption of ferrous sulphate when given in solution. There were no significant differences in the absorption of iron from the tablets used in the present study.

The absorption of iron from the rapidly-disintegrating ferrous sulphate tablets was not statistically different from that from the ferrous sulphate solution. Another study with ferrous sulphate tablets (Boye et al 1976) showed that the absorption of iron from tablets administered in solution and in tablet form was not significantly different in the present study, but the results are not comparable.

The ferrous sulphate and ferrous carbonate (I and III) contain no ascorbic acid. The addition of ascorbic acid as a reducing agent is not necessary as that from the ferrous sulphate solution. The addition of ascorbic acid (I and III) (Brise & Hallberg 1970) has been shown to increase the absorption of ferrous sulphate and ferrous carbonate.

The maximal increase of serum iron after the rapid disintegration of the tablets was not significantly different. Thus, there were no significant differences in the absorption properties of the tablets. The absorption of iron from the tablets was not significantly different.

When studying the absorption of iron from the tablets, the maximal increase of serum iron after the other tablets was not significantly different. Thus, there was no significant delay of the absorption of iron from the tablets compared with the ferrous sulphate solution. The reason for this may have been that the absorption of iron from the rapidly-disintegrating and slow-release tablets was not significantly different. The reason for this may have been that the absorption of iron from the tablets was not significantly different.

absorption are performed by non-radioactive methods using comparative studies of radioactive iron tablets and it may thus be difficult to compare the absorption of disintegrating and dissolvable unlabeled tablets. These studies will not be very

good correlation was measured in a whole-body iron after an orally administered preparation. The applicability of the results to tablets with different dissolution characteristics has never been studied. This study compared rapidly-disintegrating and slowly-dissolving tablets. A slow-release preparation was also included in

rapidly-disintegrating tablets and simulated gastric juice. The absorption of ferrous carbonate tablets in simulated gastric juice was the same as that of the tablets after 1 hour and nearly the same as that of the slow-release tablets. The rate was in agreement with that of the slow-release tablets (Duroferon® Durules®). The results from the whole-body counter, from the serum iron concentrations was the same as from the absorption from the tablets. The results were significantly

The lower absorbability of iron in blood donors in accordance with the findings of iron in blood donors of 30 mg iron t.i.d. in the same study. No significant differences

in the absorption from tablets of ferrous carbonate and ferrous sulphate when given to blood donors in doses of 10 and 100 mg iron. Differences in the materials and/or the dissolution properties of the tablets used in the various studies might explain the diverging results.

The absorption from the slow-release ferrous sulphate tablets was not statistically different from that of ferrous sulphate in solution. Another study with the same slow-release iron preparation showed a significantly increased absorption compared to rapidly-disintegrating tablets (Boye et al 1976). In this study, however, repeated doses were administered and the daily dose was 1 tablet b.d. and, unlike in the present study, the subjects were not fasting when taking the iron tablets.

The ferrous sulphate solution used in the present study (series II and III) contained 100 mg ascorbic acid per 100 mg iron. There were no indications of an absorption-promoting effect of this amount of ascorbic acid as the absorption from this solution was about the same as that from the dissolved ferrous sulphate tablets containing no ascorbic acid (series I). This is in agreement with the findings of Brise & Hallberg (1962) of a significant absorption-promoting effect of ascorbic acid only when the ratio between the amount of ascorbic acid and ferrous iron exceeded 3:1.

The maximal increase of serum iron occurred at about the same time after the rapidly-disintegrating tablets as after iron in solution. Thus, there were no indications that the disintegration or dissolution properties of these tablets were rate-limiting factors in the absorption of iron.

When studying the slow-release ferrous sulphate tablets the serum iron concentrations were followed for 8 hours instead of 6 hours as after the other tablets, as it was expected that the maximal increase of serum iron might be reached later. There was, however, no significant delay of the time for the maximal increase after the slow-release tablets compared to the solution or the rapidly-disintegrating tablets. The reasons for this are not known, but one explanation might have been that the in-vivo dissolution of iron from the rapidly-disintegrating and slow-release tablets was similar. However, in a study on the release of iron in vivo from the same rapidly-disintegrating and slow-release ferrous sulphate tablets by a scanning technique large differences were found in the release rates (Alpsten et al

1976). Thus, a more rapid release of iron in vivo than in vitro from the slow-release tablets cannot explain the similar rate of absorption as judged from the increase of serum iron. Another explanation might be that in these normal individuals the main part of the absorbed iron from the slow-release tablets emanates from iron released during the first few hours.

The relationship between the maximal increase of serum iron and the total absorption of iron is given in Fig. 4. There was a good correlation between the two measures of iron absorption. The correlation coefficient for the total number of observations (N=58) was 0.84. As will be seen from the figure, there were no obvious differences in the relationships between the total absorption of iron and the maximal increase of serum iron between the solutions of ferrous sulphate and the different iron tablets.

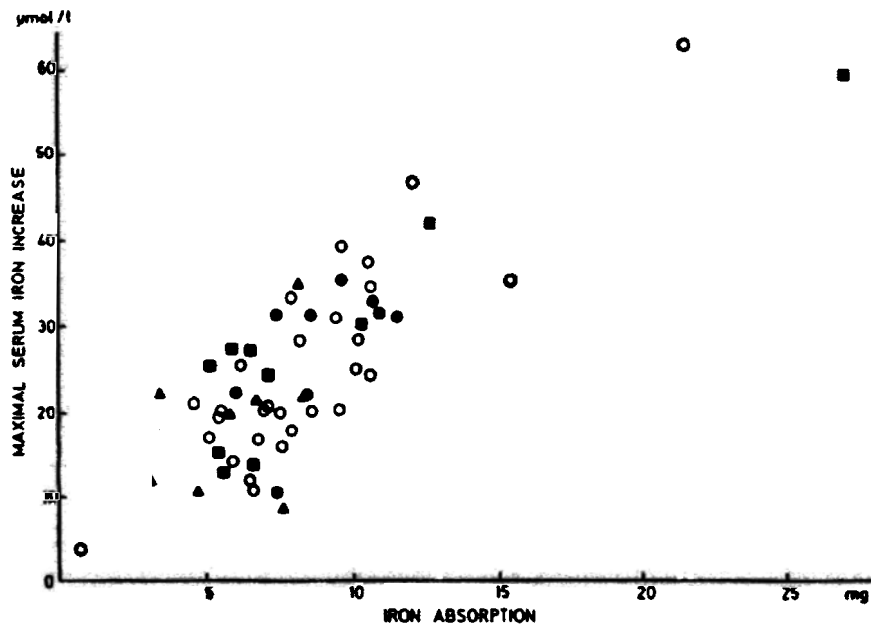


Fig. 4

Series I-II. Relationship between iron absorption and maximal increase of serum iron.

- : solution of ferrous sulphate
- : rapidly-disintegrating ferrous sulphate tablets
- : slow-release ferrous sulphate tablets
- ▲ : rapidly-disintegrating ferrous carbonate tablets

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In the ferrous carbonate series a statistically significant difference in the absorption of iron from the ferrous carbonate tablets and the solution of ferrous sulphate was found in the whole-body counter studies - $5.2\% \pm 0.8$ and $8.9\% \pm 1.1$, respectively. A numerical difference in the mean values of the maximal serum iron increase was also found - $16.0 \mu\text{mol/l} \pm 3.2$ and $25.3 \mu\text{mol/l} \pm 4.2$, respectively - but the difference did not reach statistical significance. This demonstrates that, as expected, the serum iron method is less sensitive than absorption studies with a whole-body counter. However, the present investigation has shown that serum iron studies may be used for semi-quantitative measurements of iron absorption in comparative studies on different iron preparations.

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20 25 mg

tion and maximal

tablets

tablets