Absorption of iron from ferric hydroxypyranone complexes

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(*Received 23 August 1991 – Revised 10 March 1993 – Accepted 1 April 1993*)

The absorption of ^{59}Fe from preparations of $FeSO_4$ and the ferric hydroxypyranone complexes maltol and ethyl maltol was studied by whole-body counting in normal subjects and patients with Fe deficiency. Fe in the Fe^{3+} complexes was in general absorbed almost as well as Fe^{2+}. It is concluded that the absorption of Fe^{3+} from hydroxypyranone complexes is much greater than that from simple Fe^{3+} salts; this may prove an efficient and less toxic form of Fe for the treatment of deficiency.

Iron: Ferric hydroxypyranone: Anaemia: Man

Oral Fe^{2+} preparations are widely used for treating patients with Fe deficiency. Although usually clinically effective, they are poorly and variably absorbed (Forth & Rummel, 1973), and possibly cause free-radical-mediated mucosal damage (Slivka *et al.* 1986). Dose-related side effects are common and are associated with poor compliance (Hallberg *et al.* 1966). The use of Fe^{3+} preparations should avoid these widespread problems but they are generally much less soluble at physiological pH and, therefore, have poor bioavailability. Recently the absorption of Fe^{2+} and Fe^{3+} preparations has been compared (Pagella *et al.* 1984; Dietzfelbinger, 1987; Forth & Schafer 1987; Heinrich, 1987; Schneider, 1987); in a study of fourteen different Fe preparations in man, Dietzfelbinger (1987) found that Fe^{3+} preparations were all much less bioavailable than $FeSO_4$ and, therefore, were of dubious therapeutic efficacy. Clearly an efficiently absorbed Fe^{3+} complex would be of therapeutic benefit. That such an approach may be possible is indicated by the finding that Fe associated with ferric saccharate has similar bioavailability to that of $FeSO_4$ in man (Hurrell, 1985; Hurrell *et al.* 1989). However, the precise chemical nature of this material remains undefined, it being a mixture of oligomeric Fe_2O_3 and saccharose (Hurrell, 1985) and, therefore, quality control would be difficult to monitor. In contrast, hydroxypyranones form well-defined complexes with Fe^{3+}.

Hydroxypyranones form kinetically labile Fe^{3+} complexes (Stefanovic *et al.* 1968; Gerard & Hugel, 1980) that are soluble at physiological pH. In rats the bioavailability of Fe bound to such compounds is similar to that of $FeSO_4$ (Barrand *et al.* 1987; Levey *et al.* 1988). As two of these compounds, namely maltol and ethyl maltol, are widely used Federal Drug Agency-approved food additives (Rennhard, 1971), we investigated the bioavailability of such complexes in man. We report comparisons of ^{59}Fe absorption from ferric hydroxypyranone complexes and $FeSO_4$ in both capsules and liquid preparations.

SUBJECTS AND METHODS

Subjects

Four groups of subjects were studied. First, a group of five Fe-deficient subjects (Table 1). Women likely to conceive were excluded; none was currently being treated with oral Fe. A second group of subjects was undergoing regular venesection for polycythaemia. They were Fe-deficient, although haemoglobin levels were normal (Table 1). Healthy volunteers were used as controls.

No subject was studied more than twice (i.e. two preparations). The maximum dose of radioactivity administered to any subject was 147 kBq.

The Fe status of each subject was assessed from the haemoglobin (Hb) level, erythrocyte indices, particularly mean corpuscular haemoglobin (MCH), serum Fe, total Fe-binding capacity, Fe saturation and serum ferritin levels. Hb, MCH, serum Fe, percentage saturation and ferritin levels were combined in each subject to produce an 'Fe deficiency index'. Each marker outside normal ranges scored 1.

Iron absorption

Fe absorption was measured by whole-body counting. The locally constructed shadow shield counter drew the subject at constant speed between two opposed NaI scintillation detectors (125 mm diameter × 50 mm thick) 920 mm apart. An energy window was chosen to optimize the 'figure of merit' and the deleterious effects of potential drift of window size or position. This was 0·6–1·4 MeV, with a sensitivity of 1·6 counts/s (cps) per kBq (59 cps/μCi) with a source of 37 kBq (1 μCi) within 80 mm scatter.

Preliminary studies showed, by serial counting of stools in normal subjects, that almost all unabsorbed ^{59}Fe was excreted in the faeces within 3 d of ingestion. Subjects were starved for at least 4 h and then counted before taking the oral Fe dose. This produced the 'background count'. The dose of ^{59}Fe was then taken by mouth, nothing further was taken orally for 2 h, and 2–6 h later another whole-body count was performed under identical conditions. This count minus the background count produced the 'administered dose'. After 7 d the subject was recounted and the 'residual dose' obtained, again correcting for background. The percentage absorption was then calculated, allowing for the decay of ^{59}Fe:

$$^{59}\text{Fe absorbed} = \frac{\text{residual dose}}{\text{administered dose}} \times \text{decay correction} \times 100.$$

After an interval of at least 2 weeks the procedure was repeated with a second Fe preparation.

Fe was administered either as $FeSO_4$ or complexes of Fe^{3+} with the 3-hydroxy-4-pyranones maltol or ethyl maltol. These complexes were prepared by adding the hydroxypyranone to an aqueous solution of $FeCl_3$ in 1:2 or 1:3 molar ratios and adjusting the pH to 4·0. Recrystallization from water yielded homogeneous crystals of the 1:3 complex of either Tris maltol Fe^{3+} or Tris ethylmaltol Fe^{3+}.

Experiments

Fe absorption was measured in the following experiments with 10 mg Fe and 73 kBq (2 μCi) ^{59}Fe. All percentage absorption values are given as means and standard deviations. (1) Oral solutions of 1:3 ferric maltol or $FeSO_4$ in either milk (n 2; Fe-deficient) or chicken soup (n 7; two normal, five Fe-deficient; Table 1). (2) Oral solutions of 1:3 ferric ethyl maltol or $FeSO_4$ in distilled water (n 5; Fe-deficient; Table 1). (3) Oral solutions of 1:2 ferric maltol and $FeSO_4$ (n 5; normals; Table 2).

Table 1. *Absorption of iron from ferrous sulphate and ferric complexes administered in the form of soup, milk or in distilled water to normal subjects and patients with Fe deficiency**

(Mean values and standard deviations)

Subject no.	Age (years)	Sex	Diagnosis	Deficiency index	Absorption (%) $FeSO_4$	Absorption (%) Ferric maltol (1:3)	Absorption (%) Ferric ethyl maltol (1:3)
Soup							
1	31	M	Normal	0/5	12·2	7·7	
2	45	M	Normal	0/5	5·9	6·8	
3	65	M	Colitis	2/5	25·5	25·8	
4	73	M	Partial gastrectomy	3/5	43·2	29·9	
5	48	F	Menstrual irregularity	1/5	13·2	6·4	
6	72	F	Nutritional deficiency	5/5	70·0	22·6	
7	43	F	Menstrual irregularity	5/5	25·3	18·3	
Mean					35·4	20·6	
SD					22·1	9·0	
Statistical significance of difference						($P = 0·06$)	
Milk							
1	76	F	Unknown cause	4/4	11·8	13·1	
2	58	M	Polycythaemia	2/5	8·9	10·1	
Distilled water							
1	60	M	Polycythaemia	4/5	60·6		21·5
2	70	F	Unknown cause	4/5	31·2		37·2
3	64	M	Polycythaemia	4/5	77·0		44·1
4	64	M	Polycythaemia	4/5	50·4		22·9
5	71	F	Polycythaemia	3/4	41·0		18·0
Mean					52·0		28·7
SD					17·7		11·3
Statistical significance of difference						($P < 0·05$)	

* For details of procedures, see pp. 204–206.

Table 2. *Absorption of iron from ferrous sulphate and ferric maltol (molar ratio 1:2) administered in the form of soup, milk or in distilled water to normal subjects**

Age (years)	Sex	Diagnosis	Deficiency index	Absorption (%) $FeSO_4$	Absorption (%) Ferric maltol (1:2)
55	M	Normal	0/5	5·0	2·8
45	M	Normal	0/5	6·9	10·0
31	M	Normal	0/5	17·7	13·0
31	M	Normal	0/5	16·0	8·0
24	M	Normal	0/5	16·1	14·3
Mean				12·3	9·6
SD				5·9	4·5
Statistical significance of difference			Not significant		

* For details of procedures, see pp. 204–206.

Maltol and ethyl maltol can combine with Fe^{3+} in different ratios, namely 1:1, 1:2 and 1:3. Over the pH range 6·0–9·0 the non-charged 1:3 complex predominates (Hider & Hall, 1991), but at the acid pH values in the stomach the positively charged 1:2 complex becomes the major form. Ferric maltol or ferric ethyl maltol were mostly given as the 1:3 complex, which will dissociate to the 1:2 complex in the acid lumen of the stomach and may not reform in the duodenum. In order to assess the effects of this dissociation five normal subjects received 1:2 ferric maltol solutions, and the absorption of Fe from this preparation was compared with that from a solution of $FeSO_4$ (Table 2).

Results are expressed as means and standard deviations, and the significance of the results was compared by Student's paired two-sided *t* test on logarithmically transformed dot plots since the data were skewed.

Ethical considerations

Informed written consent was obtained from all subjects and the protocol was approved by the St Thomas' Hospital Ethical Committee and the DHSS Administration of Radioactive Substances Advisory Committee.

RESULTS

When $FeSO_4$ and ferric maltol were taken with milk or soup, absorption from the two preparations was similar (Table 1). Thus, the percentage Fe absorption in the Fe-deficient subjects taking soup was 35·4 (SD 22·1) *v.* 20·6 (SD 9·0) ($P = 0{\cdot}06$) for sulphate and maltol respectively. The efficiency of absorption from water was higher (Table 1), the mean percentage Fe absorption for $FeSO_4$ and ferric ethyl maltol reaching 52·0 (SD 17·7) *v.* 28·7 (SD 11·3) ($P < 0{\cdot}05$) respectively (Table 2).

In normal subjects the absorption of Fe from solutions of ferric maltol given as the 1:2 complex and from $FeSO_4$ solutions was similar (Table 2).

DISCUSSION

The absorption of Fe from ferric maltol and ferric ethyl maltol was comparable with that from $FeSO_4$, a finding that contrasts markedly with most other Fe^{3+} preparations (Dietzfelbinger, 1987; Heinrich, 1987). Absorption from the 1:2 and 1:3 complexes was similar. A similar result, in which the rise in serum levels was measured (Crosby & O'Neil-Cutting, 1984), was obtained in another study using both 10 and 60 mg doses of Fe as ferric maltol (Kelsey *et al.* 1991).

As ferric maltol is much less likely than $FeSO_4$ to generate hydroxyl radicals, or to bind non-specifically to membrane surfaces or proteins, it is predicted to lack many of the side effects commonly experienced with $FeSO_4$ in pharmacological doses. In the present study the Fe complexes were well tolerated and, indeed, one volunteer has taken 360 mg and 720 mg Fe as ferric maltol without side effect. Similarly, because ferric maltol does not generate strong acid on hydrolysis it is less likely than $FeSO_4$ to cause acute toxicity in overdose.

We are grateful to the British Technology Group and to the Special Trustees of St Thomas' Hospital for their support, and for the help of the Department of Nuclear Medicine, and of Mr S. Batchelor and Professor T. Pearson, Departments of Medical Physics and of Haematology, St Thomas' Hospital.

REFERENCES

Barrand, M. A., Callingham, B. A. & Hider, R. C. (1987). Effects of the pyrones, maltol and ethylmaltol, on iron absorption from the rat small intestine. *Journal of Pharmacy and Pharmacology* **39**, 203–211.

Crosby, W. H. & O'Neil-Cutting, M. A. (1984). A small dose iron tolerance test as an indicator of mild iron deficiency. *Journal of the American Medical Association* **251**, 1986–1987.
Dietzfelbinger, H. (1987). Bioavailability of bi- and trivalent oral iron preparations. *Arzneimittel Forschnung* **37**, 107–112.
Forth, W. & Rummel, W. (1973). Iron absorption. *Physiological Reviews* **53**, 724–794.
Forth, W. & Schafer, S. G. (1987). Absorption of di- and trivalent iron. *Arzneimittel Forschnung* **37**, 96–100.
Gerard, C. & Hugel, R. P. (1980). Iron complexes of maltol. *Journal of Chemical Research* 3927–3954.
Hallberg, L., Ryttinger, L. & Solvell, L. (1966). Side effects of oral iron therapy. *Acta Medica Scandinavica* **181**, 3–10.
Heinrich, H. C. (1987). Intestinal absorption of ^{59}Fe from neutron-activated commercial oral iron(III)-citrate and iron(III)-hydroxide-polymaltose complexes in man. *Arzneimittel Forschnung* **37**, 105–107.
Hider, R. C. & Hall, A. D. (1991). Clinically useful chelators of tripositive elements. *Progress in Medical Chemistry* **28**, 41–173.
Hurrell, R. F. (1985). In *Iron Fortification of Foods*, pp. 44–45 [F. M. Clydesdale and K. L. Wiemer, editors]. London: Academic Press.
Hurrell, R. F., Furniss, D. E., Burri, J., Whittaker, P., Lynch, S. R. & Cook, J. D. (1989). Iron fortification of infant cereals; a proposal for the use of ferrous fumarate or ferrous succinate. *American Journal of Clinical Nutrition* **49**, 1274–1282.
Kelsey, S. M., Hider, R. C., Blair, J. R., Blake, D. R., Gutteridge, C. N. & Newland, A. C. (1991). Absorption of low and therapeutic doses of ferric maltol, a novel ferric iron compound, in iron deficient subjects using a single dose iron absorption test. *Journal of Clinical Pharmacy and Therapeutics* **16**, 117–122.
Levey, J. A., Barrand, M. A., Callingham, B. A. & Hider, R. C. (1988). Characteristics of iron(III) uptake by isolated fragments of rat small intestine in the presence of the hydroxypyrones, maltol and ethylmaltol. *Biochemical Pharmacology* **37**, 2051–2057.
Pagella, P. G., Bellavite, O., Agozzino, S. & Dona, G. C. (1984). Pharmacological and toxicological studies on an iron succinyl-protein complex (ITF282) for oral treatment of iron deficiency anaemia. *Arzneimittel Forschnung* **34**, 952–958.
Rennhard, H. H. (1971). The metabolism of ethyl maltol and maltol in the dog. *Journal of Agriculture and Food Chemistry* **19**, 152–154.
Schneider, W. (1987). The fate of iron compounds in the gastrointestinal tract. *Arzneimittel Forschnung* **37**, 92–95.
Slivka, A., Kang, J. & Cohen, G. (1986). Hydroxyl radicals and the toxicity of oral iron. *Biochemical Pharmacology* **35**, 553–556.
Stefanovic, A., Havel, J. & Sommer, L. (1968). On the reaction of iron(III) with maltol. *Collection of Czechoslovak Chemical Communications* **33**, 4198–4214.

Printed in Great Britain