A COMPARATIVE STUDY OF THE USE OF FERRIC CHELATE IN IRON-DEFICIENCY ANAEMIA

BY

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This paper presents a report on the response of iron-deficient children and young adults to three haematinics. The investigation was designed to compare established iron preparations with a recently introduced iron chelate compound in the way suggested by Cope *et al.* (1956).

Ferrous gluconate ("ferlucon") and ferrous succinate ("ferromyn") in elixir form were chosen as the established preparations. "Sytron" elixir, then on clinical trial, is a ferric sodium salt of ethylenediamine tetraacetic acid (E.D.T.A.), and has the following structural formula :

Present Investigation

The subjects were selected from the patients in a hospital for mentally deficient children; they comprised severe mental defectives of both sexes aged 5 to 18 years. Initially, 250 patients were screened by capillary haemoglobin estimations, and those with a level below 11.5 g./100 ml. were included in the trial. Almost all of these patients were completely helpless, and had to be fed by the nursing staff: that only 30 qualified for inclusion is a tribute to the patience and devotion of the sisters and nurses.

The subjects were divided into three groups of 10 each, the groups being matched as closely as possible according to age and sex. Each group received one of the haematinics for six weeks; at the end of this period, therapy was stopped. The dose was determined according to age and the utilization factor of the haematinic used (Table I).

TABLE I.—Doses Given

Drug	Age in Years	Dose	Dose in mgms.	Daily Elemental Iron (mg.)	Utilization Factor	Daily Utilization (mg.)
Ferric chelate	5-10 11-18	2 dr. b.d. 2 dr. t.d.s.	600 b.d. 600 t.d.s.	142.0 213.0	Regarded as ferrous sulphate = 14%	{ 19.9 29.8
Ferrous succinate	5-10 11-18	½ dr. t.d.s. 1 dr. b.d.	75 t.d.s. 150 b.d.	52.5 70.0	42% (Nelson, 1955)	{ 22.4 29.4
Ferrous gluconate	5-10 11-18	1 dr. b.d. 1 dr. t.d.s.	300 b.d. 300 t.d.s.	68.0 102.0	28% (Haler, 1952)	{ 19.0 28.5

As no utilization factor has yet been determined for ferric chelate, it was assumed to be the same as ferrous sulphate—that is, 14% (Witts, 1936).

Haemoglobin, packed cell volume, and mean corpuscular haemoglobin concentration values were determined before, at the end of, and four weeks after the trial period. Additional haemoglobin readings were taken at weekly intervals to obtain the rate of response. It was not possible to perform estimations eight weeks after the finish of the trial, because maintenance iron therapy was started before this interval had elapsed.

The presence of E.D.T.A. in the sytron elixir, though in small quantities, raised the question of its action upon the blood coagulation mechanisms. In order to assess the possible effect of minimal absorption of versene,

prothrombin activities were carried out on this group in the middle and at the end of the trial period, and four weeks after, using the other groups as controls.

Results

Haematological Response.—Table II shows in detail the response of individual patients. It will be seen that all had a satisfactory response, as shown by a rise in the

TABLE II.—Haematological Response

Case No.	Sex and Age	Before Trial			At End of Trial			Average Weekly Hb Rise (g./100 ml.)	Total Hb Rise (g./100 ml.)	Four Weeks After Trial		
		Hb. (g./100 ml.)	P.C.V. %	M.C.H.C. %	Hb. (g./100 ml.)	P.C.V. %	M.C.H.C. %			Hb. (g./100 ml.)	P.C.V. %	M.C.H.C. %
Ferric Chelate												
1	M 5	9.6	35	27	11.8	41	30	0.37	2.2	11.4	38	30
2	M 12	10.5	39	27	—	—	—	—	—	—	—	—
3	M 11	8.3	32	26	12.1	40	31	0.63	3.8	12.0	39	31
4	F 17	9.6	35	27	13.6	46	30	0.67	4.0	13.6	43	31
5	F 18	11.1	38	29	12.2	39	31	0.18	1.1	12.3	36	34
6	F 14	10.4	38	27	15.1	47	32	0.78	4.7	14.1	44	32
7	F 14	10.5	36	29	12.7	40	31	0.37	2.2	12.6	38	33
8	F 9	6.6	27	24	12.5	42	30	0.98	5.9	12.6	40	32
9	F 8	8.9	32	28	13.0	40	32	0.68	4.1	12.0	37	32
10	M 8	9.4	36	26	12.2	39	31	0.48	2.8	12.0	36	33
Ferrous Succinate												
11	M 6	10.5	37	28	12.0	38	32	0.25	1.5	11.7	35	33
12	M 9	11.2	38	29	12.6	38	33	0.23	1.4	12.0	35	34
13	M 8	10.4	37	28	12.6	38	33	0.37	2.2	12.0	37	32
14	F 18	11.7	41	28	13.6	41	33	0.31	1.9	13.6	45	31
15	F 14	10.5	36	29	12.4	38	33	0.31	1.9	12.7	41	31
16	F 11	6.6	26	25	10.6	34	32	0.67	4.0	11.1	35	32
17	F 5	9.6	33	29	12.2	37	33	0.40	2.6	11.4	32	31
18	F 12	9.3	33	28	—	—	—	—	—	—	—	—
19	F 10	9.0	32	28	10.8	32	34	0.30	1.8	10.4	29	35
20	M 16	9.4	36	26	13.4	42	32	0.67	4.0	12.7	41	31
Ferrous Gluconate												
21	M 13	10.2	36	28	12.8	42	31	0.43	2.6	12.6	41	31
22	M 16	10.5	39	27	13.2	44	30	0.45	2.7	13.0	42	31
23	M 7	11.4	41	28	13.0	43	30	0.27	1.6	11.7	39	30
24	F 5	10.5	37	28	12.3	40	31	0.30	1.8	12.5	40	31
25	F 11	8.9	32	28	10.6	34	31	0.28	1.7	11.2	34	33
26	F 18	11.2	38	29	13.2	44	30	0.33	2.0	13.6	43	32
27	F 14	9.0	35	26	12.6	43	30	0.60	3.6	12.9	42	31
28	F 8	10.9	39	28	11.4	38	30	0.08	0.5	12.1	39	31
29	F 10	10.4	37	28	12.5	41	31	0.35	2.1	12.1	40	31
30	M 9	9.4	35	27	12.1	39	31	0.45	2.7	12.0	36	33

M.C.H.C. The average weekly haemoglobin rise and the total increase of haemoglobin in each patient over the period of the trial are also shown. These last values have been averaged for each group, and are shown in the Figure. From this it will be seen that the mean weekly haemoglobin rise is as follows: ferric chelate, 0.57 g./100 ml./week; ferrous succinate, 0.40 g./100 ml./week; and ferrous gluconate, 0.35 g./100 ml./week. There is a signi-

ificantly greater rise in the patients taking ferric chelate than in the other two groups ($0.05 > P > 0.02$). The difference between the other two groups is not significant.

Prothrombin Times.—In the group of patients taking the ferric chelate there was a prolongation of prothrombin time (as estimated by Quick's one-stage method) of 0.5 second after three weeks of treatment in three patients, and of 0.5 to 1 second after six weeks in five patients. All patients had returned to normal values four weeks after cessation of treatment. None of the patients taking ferrous succinate or gluconate showed any such alteration of prothrombin time.

Side-effects.—Diarrhoea or vomiting, or both, appeared in three patients taking ferric chelate. Cases 1 and 10 had moderate diarrhoea during the first week of the trial, but this cleared spontaneously without treatment or withdrawal of the drug. Case 2 developed severe diarrhoea and vomiting during the second week of the trial, necessitating withdrawal of the drug and vigorous rehydration therapy. Pathogens were never isolated, but in view of the severity and the timing of the attack it may be that it was not due entirely to the drug. It was not thought justifiable to reintroduce the drug after this patient's recovery. Case 28, receiving ferrous gluconate, had mild diarrhoea during the first week. Side-effects were not observed in the patients taking ferrous succinate, but in Case 18 death occurred from pneumonia during the fourth week of the trial.

Discussion

The group of patients receiving ferric chelate showed a significantly greater response to treatment than did the other two groups. They were, however, receiving very much larger quantities of elemental iron (Table I), because the utilization factor used to calculate the dose was an assumed one only. It seems likely that this assumed 14% utilization was too low, and that this accounts for the superior response. That an organic ferric salt should have such a good utilization factor is of interest, and is in marked contrast with inorganic ferric salts. It will also be noted that the dose of ferrous succinate administered was half of that normally recommended (Gillhespy, 1955), yet had as good a therapeutic effect as ferrous gluconate given in standard dosage (Hein and Keibl, 1950). The choice of iron preparation for a given patient would appear to be governed less by pharmacological considerations than by such factors as gastric tolerance, and, especially in children, palatability, together with the comparative cost of dispensing.

The slight prolongation of the prothrombin time observed in half of those taking ferric chelate is difficult to explain. Prolonged hypocalcaemia has been observed in rabbits following intravenous E.D.T.A. (Watson and Blackburn 1956), but serum calcium levels cannot be affected in man by very large oral doses of the drug (Spencer *et al.*, 1956). Although the small alteration in prothrombin time seen in this group is apparently of no clinical significance, its cause has yet to be determined.

The higher incidence of diarrhoea and vomiting in the group taking ferric chelate must also be noted. This is no isolated occurrence, since it was found in preliminary trials with the drug; large doses were taken by my colleagues and myself over several weeks, and all noted some diarrhoea. Prothrombin times were not reduced by more than the one second reported in this trial. The diarrhoea may in part be explained by the relatively large amounts of iron in the doses given, and it would seem reasonable to suggest that doses of ferric chelate lower than those used in this trial would produce an adequate haematinic response, with a reduction in side-effects.

Summary and Conclusions

A group of 30 children and young adults with iron deficiency were treated with elixirs of ferric chelate, ferrous gluconate, and ferrous succinate. Those receiving the ferric chelate showed a significantly greater re-

sponse in haemoglobin rise compared with the other two groups, but this was probably due to the larger amount of utilizable iron given. Diarrhoea was more prominent, and there was some lowering of the prothrombin activity in half of this group, though not of sufficient degree to be of clinical importance. The dose of ferric chelate could probably be reduced below that given in this trial and still give an adequate haematological response but with a lessened likelihood of side-effects.

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TREATMENT OF ANTICHOLINESTERASE POISONING

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The recent work in this Establishment (Childs *et al.*, 1955; Askew, 1956, 1957) which has been concentrated upon the search for a practical chemotherapy in organophosphate poisoning has resulted in the development of a combined treatment with 2-hydroxyimino-methyl-N-methyl pyridinium iodide (P.A.M.) and atropine. This has been shown to be effective in all the common laboratory species and against several times the LD₅₀ of the more toxic organophosphates and to eliminate the necessity for artificial respiration. Recent reports from Japan (Namba and Hiraki, 1958) indicate that this treatment has now been used in organophosphate insecticide poisoning in man, in some cases with marked success.

Experiments with P2S

The latest development in these laboratories has been the use of the methane sulphonate equivalent of P.A.M., which is much more soluble than the iodide but is no less effective. We have given this the code name of P2S. Animal experiments have shown that P2S may be expected to be effective therapeutically against the common insecticides such as parathion, malathion, etc., and also against amiton when accidental poisoning has occurred in manufacture or actual use. Human tests have therefore been carried out (G. D. Wedd, H. W. Whitcher, and A. Taylor, unpublished work) in which P2S has been given by intramuscular injection of the 15% aqueous solution in doses up to 20 mg./kg. At this dosage reasonable therapeutic results have been obtained in animals. P2S has also been administered orally in capsules in doses up to 75 mg./kg. In no case have there been any deleterious effects following the administration as exemplified by clinical manifestations, by changes in E.C.G., pulse rate, or arterial blood pressure, or by alterations in the blood picture. The maximum dose of P2S so far given experimentally to one man has been 4.5 g. by mouth followed by 1 g. intramuscularly three hours later.