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RELATIVE ORAL TOXICITY OF SOME THERAPEUTIC IRON PREPARATIONS

BY

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Forbes (1947) and Thomson (1947) have recently described serious consequences in young children, including three deaths, following the unauthorized taking of ferrous sulphate tablets in excessive numbers. These and certain cases previously reported to us raised the general question of the toxicity of iron compounds when large doses were consumed orally, and also of the additional effect, if any, of the small amount of copper and manganese sulphates which were present in the tablets.

Examination of the literature failed to reveal earlier reports of ill effects from orally administered iron compounds, except for occasional references to slight alimentary disturbances. Further, and more surprisingly in view of the widespread use of iron compounds for the treatment of iron deficiency or "nutritional" anaemia, we have been unable to find any account of pharmacological investigations into the action of iron given by mouth, although its effects by injection have received some attention and it is accepted that serious ill effects may follow its absorption into the blood stream.

It therefore seemed desirable to test experimentally on several species of laboratory animal the effects of orally administering very large doses of some of the more commonly used iron preparations. For this purpose we chose ferrous sulphate, with and without the presence of the "trace" metals copper and manganese; ferrous carbonate in the form of Bland's pills; ferrous gluconate, because of the claims made for it by Reznikoff and Goebel (1937); ferric chloride, so as to include at least one preparation of ionizable ferric iron; and iron and ammonium citrate, widely used in compounded medicines, though nowadays largely replaced by ferrous sulphate for simple oral iron therapy—shown by many workers from Davidson (1933) onwards to be much more effective in haemopoiesis than the non-ionized "scale salts," when compared on an equivalent iron basis. Rabbits and guinea-pigs were used for studying the pathology and histology of any disturbances observed, and mice for the estimation of median lethal doses (LD50) with reasonable accuracy.

As a practical problem in human therapeutics we were really concerned with establishing the "therapeutic index" of ionizable iron—that is, the ratio of its median toxic dose to its median therapeutic dose. Here we encountered two difficulties, the one general and the other particular. First, it is ordinarily impossible to establish such an index for the action of a drug on the human organism, simply because data, unfortunately, are not as a rule available for the median toxic human dose. The pharmacologist therefore normally has recourse to establishing the therapeutic index of a drug on at least one species of laboratory animal, and preferably on more than one. If the value of this index is of roughly the same order for two or more species of laboratory animals it is reasonable to assume that the same value will apply to man; in general, experience bears out this assumption. However, even this line of approach was not available to us, for there is no species of animal—with the possible exception of the rat made anaemic on a milk diet—for which we have information about the median therapeutic dose of iron compounds.

We were consequently forced back on to the unsatisfactory step of relating toxic doses to the body weight of the animal used and arguing on the same basis for man. The objections to this line of reasoning, however, appear much less strong for iron compounds than they might for other drugs, for it will be seen that toxic effects—and, in particular, fatal results—were produced only by doses so immensely out of proportion to the animal's normal intake of iron as to make highly unlikely the ingestion of dangerous amounts by human subjects. The facts established by our experiments nevertheless make it clearly desirable to render access of infants and small children to iron preparations as difficult as possible. Such precautions would normally be taken with many of the common drugs to be found in the ordinary household—for example, quinine salts and acetylsalicylic acid—without in any way detracting from their value and importance in therapeutics.

Toxicity

The results obtained with the three species of animals used are summarized in the accompanying table. The

Table showing the Median Lethal Toxic Doses of Iron Compounds by the Oral Route

Compound	Iron in Preparation, Calculated as Fe	Dose per kg. of Body Weight					
		Rabbits		Guinea-pigs		Mice	
		Actual	Cal. as Fe	Actual	Cal. as Fe	Actual	Cal. as Fe
Ferrous sulphate crystals	20	3.0	0.6	1.5	0.3	4.5	0.9
Ferrous sulphate prep. with copper and manganese	24	3.0	0.72	1.25	0.3	4.1	1.0
Ferrous gluconate	16.6	3.5	0.58	2.1	0.35	6.6	1.1
Ferrous carbonate pills	12.5	17.8	2.22	16.0	2.0	31.0	3.8
Ferric chloride	34	1.2	0.4	0.6	0.2	1.5	0.5
Ferric and ammonium citrate	20	2.8	0.56	1.75	0.35	5.0	1.0

figures from tests on rabbits and guinea-pigs, owing to the relatively small numbers of such animals that can be used in toxicity tests, must be regarded as first approximations; the figures from the tests on mice have a greater accuracy, except those for iron and ammonium citrate, because with this product a great individual variation was found among the animals. Slopes of the regression curves, and the errors of estimating the LD50, which were of the order usually found in tests of this kind, were obtained by the graphical method of de Beer (1945).

It will be seen: (1) That the presence of small amounts of copper and manganese sulphates made no difference to

the toxicity of the iron or ferrous sulphate. (2) That the iron in ferrous sulphate, ferrous gluconate, and—curiously enough—iron and ammonium citrate had the same toxicity, though it must be repeated that the figure for the last compound is subject to a very large error. (3) That the iron in Blaud's pills has apparently only about one-quarter the toxicity of the other forms. It is, of course, well known that the iron in Blaud's pills has also much less therapeutic effect, and these two facts are undoubtedly due, at least in part, to the same basic phenomenon—the relative insolubility of their ferrous carbonate in gastric and intestinal contents. (4) That ferric iron appears to be up to twice as toxic as ferrous iron. We have no explanation for this finding, especially if, as is generally held, ferric iron is reduced in the stomach to the ferrous state. It must, however, be remembered that ferric chloride is a much more acidic substance than ferrous sulphate (or gluconate). The introduction of large quantities into the stomach must involve a considerable increase in gastric acidity, which in turn may hasten alimentary absorption of the iron—possibly an advantage with therapeutic doses but certainly not with toxic ones.

The observation with Blaud's pills suggested that sodium carbonate or bicarbonate might be useful as an antidote to toxic oral doses of iron compounds. Four rabbits were therefore given known toxic doses of ferrous sulphate (3 g. per kg. of body weight) and two of them then received the same amount of sodium carbonate. One of these two lived for two days, while the other survived completely; the two that did not receive sodium carbonate died overnight. This experiment was repeated twice, with similar results—a fact which points to the conclusion that sodium carbonate treatment might, if given soon enough, help to reduce the toxic effects of excessive iron doses by mouth.

Pathology and Histology

Rabbits

The rabbits used were of both sexes and weighed between 2 and 3 kg. They were fasted overnight and were then given by stomach tube doses of the iron compounds, graded and proportionate to their body weights. Two animals were used for each dose and at least ten animals for each substance. If the rabbits survived, daily samples of urine were collected for three days. Haematological examinations included differential and total counts of red and white cells and estimates of haemoglobin levels. Necropsies with examination of all major organs followed as quickly as possible after death. Sections were cut of parts of the stomach, intestine, liver, and kidneys, and were stained for iron as well as with haematoxylin and eosin.

Within a few minutes of receiving a toxic dose of iron the rabbits became prostrated. They lay on their stomachs with limbs extended, their respiratory rate increased, micturition often occurred, and reflex movement of the hind legs was considerably retarded. Coma followed, with shallow breathing and gradual disappearance of reflex movements. The animal either died two to six hours after receiving the dose (according to its size), sometimes following convulsions, or recovered.

The rabbits receiving Blaud's pills had a profuse diarrhoea. This fact, with the freedom of all other animals from this symptom, has, we believe, a very simple explanation. The pills are made by reacting ferrous sulphate with sodium carbonate, so that the ferrous carbonate formed must be accompanied by an equivalent amount of sodium sulphate. There seems no reason why a large dose of Glauber's salts should have an effect on rabbits differing from that on man. Moreover, the laxative effect of the associated sodium sulphate must have hastened the alimen-

tary passage of these large doses of ferrous carbonate: this would tend further to reduce its toxic effects.

At necropsy the stomachs usually showed congested areas with shedding of mucosa, especially at the greater curvature. The amount of damage was to a large extent determined by the size of dose: the smaller toxic doses caused only very slight damage to the stomach wall. Bleeding into the stomach was the exception rather than the rule, but it was seen after the larger doses of both ferrous sulphate and ferric chloride and in one animal that had received ferrous gluconate. The small intestines generally showed much hyperaemia in their upper regions, but here also haemorrhages were seen only after very large doses. Surviving animals showed no evidence of kidney damage, the urine being invariably devoid of abnormal constituents. There were no departures from normal blood counts. Recovery of surviving animals was usually rapid.

Changes in the histology of stomach, liver, and kidney in rabbits killed by the iron compounds were very small, and appeared insufficient to account for the death of the animals. In the stomach there was only slight necrosis of the superficial layer of the villi and deposits of iron on the mucous membrane (occasionally also in the endothelium of the smaller blood vessels). There were deposits of iron in the bile ducts, but only slight hydropic changes in the liver. In rabbits surviving and killed three days after dosing we observed small foci of fatty degeneration, and necrosis was present in the peripheral parts of the lobuli, with deposits of iron, mainly in the Kpffer cells. The other surviving animals appeared to be completely restored to normal health and activity after a few days.

Guinea-pigs

The animals used, of either sex, weighed between 200 and 300 g. Their distribution over the different dosage groups was made so far as possible to equalize the average weights of the groups. Each dose was given to at least three animals, and at least ten guinea-pigs were used for each substance tested. The animals were fasted overnight and given the appropriate dose of iron compound by dropping it into the mouth and then tickling the fauces. Necropsies, dissections, and histological work were carried out as on the rabbits.

In general the immediate consequences of excessive iron administration by mouth were the same in guinea-pigs as in rabbits. At necropsy, however, there was evidence of severer damage to the stomach; macroscopically the findings with the larger doses resembled those described by Forbes. After doses of 1.5 g. per kg. of body weight of ferrous sulphate or ferric chloride the stomach contained both fresh and changed blood; necrosis; shedding of mucosa, and areas of haemorrhage were obvious to the naked eye. Severe irritation of the stomach wall followed the ingestion of 3 g. of ferrous gluconate per kg. of body weight: in one animal the stomach was full of blood-stained material. Changes were less severe after dosing with iron and ammonium citrate or Blaud's pills, but at the larger dose levels either preparation caused well-marked irritation of gastric mucosa with occasional petechial haemorrhages.

Histological changes, as in rabbits, were slight and insufficient in themselves to account for the deaths. There was but superficial damage to the gastric villi, with deposits of iron on the mucous membrane, which also showed some areas of capillary bleeding. In a very few instances there were some fatty changes in the liver.

Necropsies were not made on mice, which were used solely to obtain a reasonably accurate estimate of the median lethal doses.

Discussion

From the experiments described there can be no doubt that in very large doses certain soluble iron salts, whether ferrous or ferric, whether of organic or inorganic acids, and whether normally ionizable or complexes of the "scale salt" type, are toxic to at least three species of laboratory animals. It is reasonable, and probably a wise precaution, by extrapolation to accept as proved that all similar iron compounds can, in excessively large doses, kill mammals of any species, including man. It must, however, be emphasized that toxic doses really are excessive. The amount of ferrous sulphate necessary to kill on the average one out of two 10-stone (63.5-kg.) men, if man's susceptibility on a body-weight basis is assumed to be the same as that of the rabbit, would represent at least several hundred tablets of 3 gr. (0.2 g.) of exsiccated ferrous sulphate, each containing 1 gr. (65 mg.) of iron. Obviously the number may be considerably smaller for infants and young children, being reckoned in tens rather than hundreds.

The similarity in behaviour of various iron preparations suggests that after solution in the stomach they are all reduced to the ferrous state and that ferrous iron when present in very large amounts, whether wholly ionized or not, is alone responsible for the damage. Ferrous sulphate should be completely ionized at high concentrations, and ferrous gluconate probably hardly ionized at all even at low concentrations, yet they show indistinguishable toxicities in very high doses. It may be remarked, in passing, that none of the ionizable iron compounds exists as such in the stomach after therapeutic doses: apart from un-ionized hydrochloric acid in the gastric contents, there will then be present in solution the chloride, sulphate, and other anions, the hydrogen, iron, and other cations, and the various un-ionized soluble constituents. Forbes's contrasting of ferrous sulphate with ferrous chloride in solution therefore seems to be misleading even when the sulphate has been ingested at much above the therapeutic level.

The post-mortem and histological examinations have furnished no positive information about the *modus operandi* of iron at orally toxic levels. A decision between shock due to tissue damage—which at worst was not very great and appeared rapidly reversible in the milder cases—and systemic effects following passage of excess iron into the blood stream cannot be made on the basis of our experiments. They were, in any event, carried out with an immediately practical object—to find and record at what doses therapeutic iron preparations could exert toxic effects on experimental animals. The results of these experiments are reassuring. They show, at any rate in so far as the experimental animals react similarly to man, that the gap between curative and harmful doses of iron compounds is very large—and obviously still larger between preventive and fatal doses. Indeed, I doubt if there are many medicinal substances with so large a "therapeutic index." The upper dose of ferrous sulphate, according to the *British Pharmacopoeia*, is 0.3 g., which would be contained in five tablets of the product causing fatalities that led to this investigation. In few circumstances is it likely that an adult would be recommended to take more than 12 such tablets a day, and the results suggest the harmlessness of anything less than several hundred tablets taken all at one time and on an empty stomach. It is, however, desirable that physicians and pharmacists should warn parents and adults generally that iron preparations should be kept out of reach of the very young.

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AN EXPERIMENT IN REHABILITATION

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During the recent war, with its urgent demands for manpower, the attention of the medical services was sharply focused on to an aspect of clinical treatment that had under less pressing conditions been of relatively secondary importance. The economic aspect of medical or surgical treatment assumed an importance equal to that previously held by the somewhat ambiguous criterion of a "good clinical result." This is none the less true of to-day. The essence of the problem facing the clinician from the first day of treatment onward can best be expressed in the form of the question: How may this man be returned to his accustomed way of life and employment with a minimum loss of time and skill? The answer to that question embodies the full significance of the term "Rehabilitation," which must include the repair of the injury as well as the restoration of functional efficiency.

In industry to-day there are several examples of the successful handling of the problem of rehabilitation of the injured workman by a close liaison between medical and industrial authorities, the responsibility of treatment being shared equally between the two. Such schemes are at the present time too elaborate and costly to be undertaken by the smaller concerns. In this paper we have briefly described an experimental rehabilitation scheme carried out during wartime. We have attempted to underline the principles of treatment and to show how such a scheme may be applied to the industrial injuries of peacetime, with the minimum of special equipment, under existing factory conditions.

The Scheme

During 1945 and 1946, thanks to the co-operation of a near-by aircraft factory, a number of long-term Service and ex-Service cases drawn from the orthopaedic, plastic, and peripheral nerve injury units of Hill End Hospital were sent to work in the factory in chosen occupations. The choice of Service men, the majority complete strangers to factory life, was governed partly by the preponderance of Service casualties and partly by the special problem that they offered. As already stated, they were mainly "long-term" cases requiring a series of reconstructive operations or a long course of physiotherapy. It was thought that this experiment might have the double advantage of providing selected remedial exercises and, at the same time, a much-needed change of surroundings.