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IRON METABOLISM IN TETRACYCLINE-TREATED ACNE PATIENTS

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Abstract. Iron and tetracyclines form insoluble chelate compounds. Thus it was found in a pilot study that iron was not absorbed from the gastrointestinal tract after peroral administration together with tetracycline; both drugs were given in water solution. However, in a long-term study of 55 patients with acne vulgaris treated with tetracycline no development of iron deficiency or anemia was found, although the patients were young females, a population often having a negative iron balance. It is concluded that absorption of organic iron present in food is not significantly influenced by tetracyclines.

It has been known for several years that di- and trivalent metal ions decrease resorption of tetracyclines (3, 12, 13). This probably occurs by the formation of insoluble chelate compounds between the tetracyclines and the metal ions (1). Such a complex formation between tetracyclines and iron probably explains the recent finding that concomitant therapy with iron and tetracyclines leads to decreased serum concentrations of tetracyclines (4, 11).

Long-term therapy with relatively low doses of tetracycline has proved to be of benefit to many patients with acne (2, 10). The apparent side effects in these dosages (150–500 mg tetracycline daily) seem to be few (10). However, as iron and tetracyclines form insoluble complexes causing a poor absorption of the tetracyclines it might well be expected that the opposite also holds true, i.e. tetracyclines might inhibit the absorption of iron. Patients treated with tetracyclines for long periods, as in acne vulgaris, would thus risk getting sideropenia.

The purpose of the present investigation was primarily to see whether the absorption of a single dose of iron is inhibited by simultaneous administration of tetracycline. When this had been established the next step was to study the effect of long-term therapy with tetracyclines in iron metabolism in acne patients in order to find out whether the patients develop iron deficiency.

MATERIAL AND METHODS

Single dose experiment. Iron absorption was studied in 3 patients with the aid of radioactive iron and a whole body counter. The method used has been described in detail elsewhere (6). After the radioactive background of the patient has been measured in the whole body counter, a test dose of a water solution of ferrous sulphate containing 0.25 mg ferrous iron labelled with 0.5 μCi ^{59}Fe is administered orally after an overnight fast. One hour after the administration of the test dose, the total body radioactivity is measured to establish the so-called 100% value. Another whole body count about 2 weeks later measures the retention of the radioactivity within the body and the percentage absorption of the test dose may be calculated.

After the iron absorption value had been established the effect of tetracyclines on the absorption of iron was studied. Immediately after the test dose of iron, 20 ml of a solution containing tetracycline sodium hexametaphosphate corresponding to 20 mg tetracycline chloride/ml was administered. Thus a dose of 400 mg was given. The 100% value and the retention value were measured as described above.

Long-term study. In female patients with acne vulgaris, in whom tetracycline therapy was instituted, during the period Sept. 1971 to Febr. 1972, hemoglobin, serum iron, and transferrin were determined before starting the therapy with tetracyclines and then every month or every second month as long as tetracyclines were given. The patients were followed till June 1972. The patients received tablets containing tetracycline hexametaphosphate corresponding to 250 mg tetracycline hydrochloride (Tetradecin Novum, Astra, Södertälje, Sweden). The dosage as a rule was 1 tabl. 4 times a day during the first week; then 1 tabl. twice a day. Only patients who had been without tetracyclines for at least 3 months were included. The study included 55 female patients aged 15 to 50 years, 27 of the patients were between 15 and 19 years, and 19 between 20 and 29 years (Fig. 1).

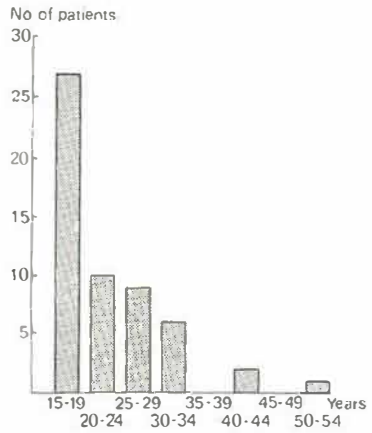

Fig. 1. Age distribution of the 55 patients.

Hemoglobin, serum iron, and transferrin were determined with ordinary routine methods. Iron absorption was studied with a whole-body counter according to the method described earlier.

RESULTS

Single-dose experiment. Two iron absorption studies were performed with a 2 week interval. The tetracycline solution was administered immediately after the iron test dose on the second occasion. In the three cases studied the absorption of iron together with the tetracyclines was greatly reduced (Table I).

Long-term study. Fig. 2 summarizes the results of the 55 patients. Most patients were not fasting at their first visit and were asked to return in a few days to give blood samples, but some did not show up and blood samples were thus not given until the next visit to the clinic 1–2 months later. This explains why a starting value is not obtained in all patients. No influence was found on the peripheral blood values.

Table II shows the peripheral hematological

Table I. *Absorption of a single dose of iron given alone and together with tetracycline*

Subject	Iron absorption, per cent of 0.25 mg Fe^{++}	
	Iron test dose alone	Iron test dose and Tetracycline solution
B.-M. C.	40.7	1.2
I. H.	32.3	2.8
M. H.	55.4	0.9

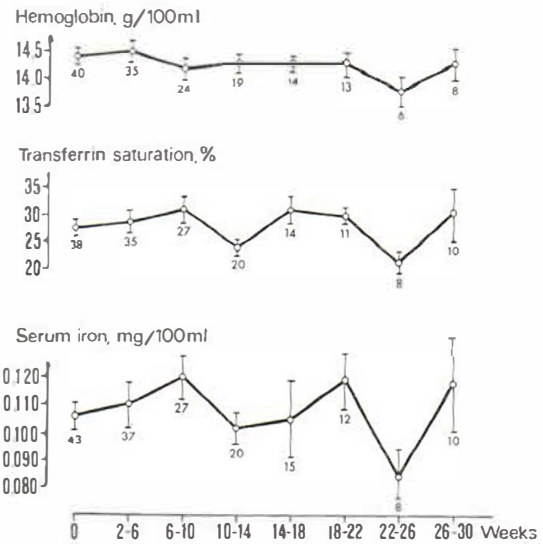

Fig. 2. Hemoglobin concentration, transferrin saturation and serum iron concentration during long-term treatment with tetracyclines. The figures at each point denote the number of subjects studied.

values in detail for the 10 patients who were followed for as long as 26–30 weeks. No indications of anemia or sideropenia were observed.

In 9 patients iron absorption was studied before tetracycline therapy and after 12–23 weeks (mean 19 weeks). Table III shows the iron absorption values before and after therapy. It is shown that virtually no changes in iron absorption had occurred.

Table II. *Individual blood values before and after treatment with tetracycline in the 10 patients treated for 26–30 weeks*

	Hemoglobin (mg/100 ml)		Serum Fe (mg/100 ml)		Fe-saturation (%)	
	Before	After	Before	After	Before	After
	14.1	13.4	0.098	0.085	29	25
	—	—	0.147	0.121	32	32
	14.1	15.0	0.109	0.206	29	56
	14.1	14.4	0.109	0.063	27	15
	13.2	15.1	—	0.088	—	19
	—	15.0	0.173	0.135	32	32
	—	14.4	—	0.045	—	12
	14.6	14.5	0.158	0.098	42	26
	14.3	12.6	0.099	0.127	24	33
	15.0	—	0.149	0.209	38	56
M±S.E.	14.2 ±0.21	14.3 ±0.31	0.130 ±0.010	0.118 ±0.017	31.6 ±2.1	30.6 ±4.8

Table III. *Iron absorption before and after tetracycline therapy in 9 patients*

	Iron absorption, per cent of 0.25 mg Fe^{++}		
	Before therapy	After therapy	Duration of therapy, weeks
	55.4	52.8	13
	35.2	25.0	23
	28.3	76.9	17
	68.0	71.0	18
	41.5	21.8	12
	58.0	66.0	18
	25.5	58.0	22
	65.4	44.0	19
	77.1	91.0	19
$M \pm$ S.E.	50.5 ± 6.2	56.3 ± 7.4	19 ± 1.2

DISCUSSION

In spite of the few subjects studied in the single-dose experiments there is no doubt that the absorption of ferrous iron from the intestine was markedly inhibited in the presence of tetracycline. The almost completely inhibited absorption of iron is comparable to that seen when the test dose is administered together with a full meal (7). The inhibiting effect of food is usually ascribed to the chelate formation between iron and various organic substances. The explanation of the effect of tetracyclines on iron absorption is probably of the same nature since it has been shown earlier that tetracyclines and divalent ions may form strong chelates (1). Greenberger et al. (5) have found that treatment of rats with high doses of tetracycline results in impaired transport of iron through the intestinal mucosa. Their data suggest that the inhibitory effect of tetracyclines on iron absorption may be due to other factors in addition to binding of iron by tetracyclines. Whether such an inhibition of the transport mechanism is involved in our single-dose experiment cannot be determined from the present data.

The long-term study comprised young females. It has been shown that young females are at great risk of developing iron deficiency because of increased iron losses during a period of life when iron intake often does not cover iron needs (8, 9). Although the patients of the present study did not develop anemia or sideropenia, it was found that in a group of these patients the initial iron absorption values were rather high, indicating the existence of a certain latent iron deficiency among these women (Table III). However, after several weeks of tetracycline therapy the iron absorption values were about the same, indicating that no further progress of the iron deficiency had taken place.

The dosage, 250 mg twice a day, is lower than that usually recommended for treatment of bacterial infections, but higher than might be necessary for treating many patients with acne vulgaris who may improve on 250 mg a day or every second day. However, in order to disclose any tendency to sideropenia developing in these patients no attempts were made in the present study to lower the dose.

The present investigation has shown that a tetracycline solution markedly inhibits the absorption of simultaneously administered iron, probably by complex formation. However, no signs of iron deficiency appeared during long-term therapy with tetracyclines, although the subjects studied belonged to a category inclined to develop iron deficiency. Thus absorption of iron from food was not impaired. It is probable that the effect of the tetracyclines is mainly seen with the iton salts and not to the same extent with the organic iron present in food.

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