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Effect of Oral Ferrous Sulphate on the Half-Life of Doxycycline in Man

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Summary. In a double-blind cross-over study in seven patients, oral ferrous sulphate (80 mg Fe^{++}) given 3, 7 and 11 h after a daily oral dose of doxycycline, lowered the serum concentration of doxycycline by 20–45%. The half-life of intravenous doxycycline was shortened from 16.6±0.7 h to 11.0± 0.4 h by concomitant oral iron therapy. These results are an indirect indication of significant intestinal secretion and reabsorption of doxycycline. The interaction between doxycycline and iron cannot be avoided completely by leaving an interval of 3 h between doses of the two drugs.

Key words: Iron, doxycycline, drug interaction, enterohepatic circulation.

Doxycycline, a lipophilic tetracycline derivative, is rapidly and almost completely absorbed from the gastrointestinal tract. Owing to its long half-life, even one dose a day suffices to maintain bacteriostatic plasma levels, provided the initial dose is adequate. Like other tetracyclines, doxycycline forms chelates with bi- and trivalent cations and its gastrointestinal absorption is seriously impaired by simultaneous intake of iron salts [7]. Such interaction with the *initial* absorption of tetracyclines can be avoided by leaving an adequate time interval between the doses of the drugs [3]. However, as oral iron salts remain largely unabsorbed in the gastrointestinal tract, they might interfere with the enteric reabsorption of tetracycline derivatives which are excreted into intestine and which might be reabsorbed because of their highly lipophilic properties [2, 8]. The aims of the present study were to investigate whether oral iron therapy would modify the half-life of doxycycline, and, if so, what would be the effects on serum levels of doxycycline during combined treatment with iron.

Patients and Methods

A double-blind cross-over study was performed in long-stay patients, aged 48–82 y, weight 50–70 kg, who volunteered for the experiment. Their usual daily treatment with digitalis and diuretics was continued unchanged throughout the experimental period. No other chemotherapeutic agents or antacids were given. They received the usual hospital diet during the study. Two separate experiments were carried out according to the following plan.

Seven patients commenced arbitrarily oral therapy either with placebo or with 400 mg ferrous sulphate (containing 80 mg Fe^{++} in gelatine capsules) at 11 a.m., 3 and 7 p.m. On the 3rd day of treatment, the patients took 200 mg of doxycycline at 8 a.m., followed by daily ingestion of 100 mg doxycycline at 8 a.m. for a further 4 days. Blood samples were taken daily between 7.30–8 a.m., i.e. just before the next dose of doxycycline and at least 3 h before the next dose of the iron compound.

In order to study the effects of iron on the half-life of doxycycline, four patients ingested either placebo or ferrous sulphate 400 mg at 11 a.m., 3 and 7 p.m., for 4 days. At 8 a.m. the 3rd day of treatment, doxycycline hydrochloride, in a dose equivalent to 100 mg of doxycycline base, was injected intravenously into a cubital vein over a period of 2–3 min. Blood samples were taken 1, 3, 5, 8, 12, 24 and 36 h after the injection of doxycycline.

The serum concentration of doxycycline was determined both fluorometrically, according to the method of Kohn [4], and microbiologically, by the agar-plate method of Bennet *et al.* [1] on Bacto Penassay Seed Agar (Difco), with Bacillus Cereus A.T.C.C. 9634 as test organism. Serum levels of doxycycline estimated fluorometrically were somewhat higher than those measured microbiologically, but the half-lives of doxycycline estimated by the two methods did not differ from one another.

The means and standard errors (S.E.) were calculated for the serum concentrations and half-lives of doxycycline. The results were analysed statistically by Student's t-test for paired values.

Results

Serum concentrations of doxycycline were 20—45% lower during combined treatment with iron than during the period of doxycycline and placebo.

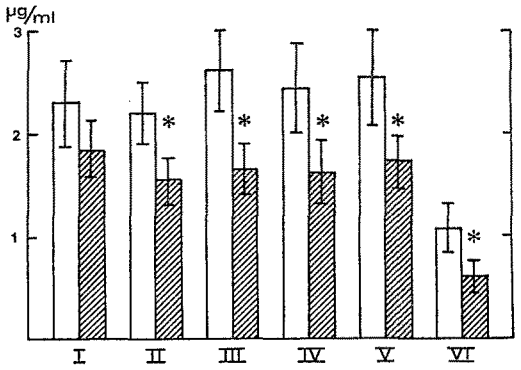

Fig. 1. Mean (±S.E.) serum doxycycline concentrations in a double-blind cross-over study in seven patients, who received either doxycycline + placebo (open bars) or doxycycline + ferrous sulphate (shaded bars). Serum concentration of doxycycline was determined fluorometrically just before the daily dose of doxycycline (I—IV), as well as 24 and 48 h after the last dose of it (V—VI). The asterisk indicates a significant difference ($p<0.05$) from the respective control

The difference was significant ($p<0.05$), even 48 h after commencement of the combined treatment, and it remained so throughout the study (Fig. 1).

The half-life of a single intravenous dose of doxycycline was shortened from 16.6±0.7 h during the control period to 11.0±0.4 h during treatment with oral iron ($p<0.02$), as shown in Fig. 2.

Discussion

The serum concentration of doxycycline was lower if the drug was taken concurrently with oral iron therapy, even though an adequate time interval was allowed between doses of the two drugs in order to allow for the absorption of doxycycline [3]. Because the half-life of doxycycline given intravenously was shortened by oral iron therapy, factors other than prevention of the primary absorption of doxycycline by iron must be responsible for the interaction.

Doxycycline is concentrated and excreted with the bile into the intestinal lumen [2, 6, 8, 9]. Other intestinal fluids probably contain significant amounts of doxycycline, too, which seems likely to be re-

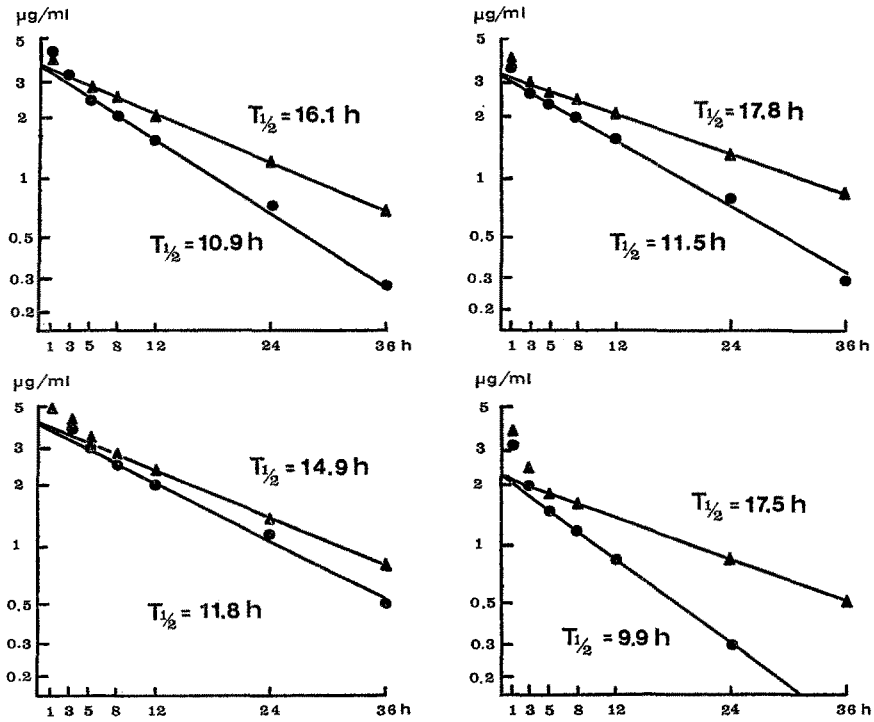

Fig. 2. Half-lives of serum doxycycline after a single intravenous injection of 100 mg of doxycycline in a cross-over study in four patients either taking iron (●—●) or placebo (▲—▲). The mean (±S.E.) half-life of doxycycline during the placebo period was 16.6±0.7 h, and during iron therapy it was 11.0±0.4 h

absorbed because of its strongly lipophilic properties [8, 9]. This mechanism, i.e. excretion into the gut and subsequent reabsorption, seems to be one factor contributing to the long half-life of doxycycline. Accordingly iron, which remains mainly unabsorbed within the intestines, could chelate with doxycycline and prevents its reabsorption. This would lead to shortening of its half-life and reduced serum levels of doxycycline. Similarly, it appears reasonable to assume that antacids, that contain aluminium, magnesium or calcium salts, might have similar effects on the half-life of doxycycline and some other lipophilic tetracycline derivatives by prevention of their enteric reabsorption.

It was shown previously [3] that interaction of iron and tetracycline can be avoided to a considerable extent by allowing an interval of 3 h between doses of these drugs. However, significant reduction of the half-life of doxycycline and lowering of its serum level was found to be caused even by such delayed treatment with an oral iron compound. These results are an indirect indication of considerable intestinal secretion and reabsorption of doxycycline in man. The reduction of the half-life of doxycycline is probably due to inhibition of intestinal reabsorption of this tetracycline derivative.

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