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Drs Briant and George reply as follows:

Our critics, Drs Tait and Todrick, are concerned that in describing Ciba 34276-Ba as a tricyclic antidepressant, we are devaluing the term (Briant & George, 1974). In reply, we would point out that the definition given by the International Union of Pure and Applied Chemists (IUPAC) applies to any chemical structure which possesses three rings. There is nothing specific about the term chemically (or therapeutically) and the compound which we have studied satisfies the definition given above.

Early studies on the use of tricyclic antidepressants (Kiloh, Ball & Garside, 1962) suggested that patients with endogenous depression responded more favourably than those with 'reactive' depression. However, many psychiatrists now feel that there is little difference in the response of the two forms of depression. Furthermore, it should be remembered that there are inconsistencies in psychiatric diagnosis, the reliability of which is discouragingly low (Cooper, Kendell, Gurland, Sartorius, & Farkas, 1969). Thus, to collect a homogeneous sample of patients with major endogenous depression may be neither possible nor relevant. Our tentative conclusion that drugs such as Ciba 34276-Ba could allow the possibility of effective antidepressant therapy without undesirable interactions at adrenoceptor sites remains.

R.H. BRIANT

Department of Medicine, The University of Auckland School of Medicine, New Zealand

C.F. GEORGE

Faculty of Medicine, University of Southampton, Southampton SO9 3TU

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INHIBITION OF IRON ABSORPTION BY TETRACYCLINE

Ferrous sulphate and other iron salts interfere with the gastro-intestinal absorption of tetracyclines in man (Neuvonen, Gothoni, Hackman & af Björksten, 1970; Neuvonen & Turakka, 1974). This effect is obviously based on the well known ability of Fe^{++} and Fe^{+++} to form stabile chelates with tetracyclines (Albert, 1953). Moreover, it has been shown that tetracycline inhibits the absorption of ferrous sulphate in rats (Greenberger, Rubbert & Cuppage, 1967). On the basis of the supposed physicochemical mechanism of interaction it was surprising that the inhibition of iron

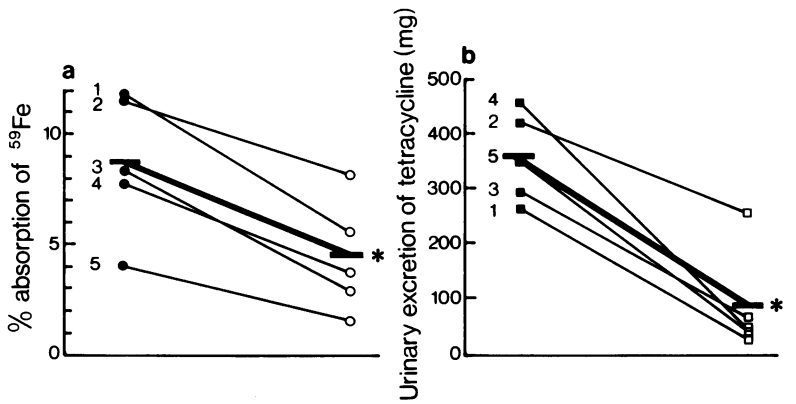

Figure 1 Mutual decrease in the gastrointestinal absorption of iron and tetracycline on their simultaneous ingestion. a: Absorption of ^{59}Fe following the administration of $^{59}FeSO_4$ (100 mg Fe^{++}) either alone (•) or together with tetracycline hydrochloride (○, 1000 mg). b: Excretion of tetracycline in urine during 48 h following the administration of tetracycline hydrochloride (1000 mg) either alone (■) or together with $^{59}FeSO_4$ (□, 100 mg Fe^{++}). The individual values for each of the volunteers (1-5) and the means (heavy line) are given. Significant difference between the means, * $P < 0.005$.

absorption by tetracycline could not be demonstrated in man (Greenberger, 1971, 1973). These seemingly contradictory results led us to perform a cross-over absorption study using labelled iron to investigate the supposed mutual interaction between iron and tetracycline in man.

Five healthy female volunteers (age 51-65 years, weight 49-76 kg) with normal haemoglobin (12.1-13.7 g/100 ml) and serum iron (98-125 μg/100 ml) and total iron binding capacity (TIBC) (336-390 μg/100 ml) participated in this study. Written informed consent was obtained. The iron was administered as tablets with the tablet disintegration time of 30 min (USP) after overnight fast either alone or together with tetracycline hydrochloride (1.0 g) in gelatine capsules. The dose of ferrous sulphate was 100 mg as Fe^{++} containing 1 μCi of ^{59}Fe. The relative high doses correspond to those used in the earlier studies mentioned (Greenberger, 1971, 1973). The interval between the two iron absorption studies was one month. The absorption of ^{59}Fe was determined by the whole body counting method (Blahd, 1971). The absorption of tetracycline was studied when tetracycline was ingested either with iron or alone two weeks after the last iron absorption study. The absorption of tetracycline was determined by measuring fluorometrically (Kohn, 1961) the excretion of tetracycline in urine during 48 h following the ingestion. In healthy persons the excretion of tetracycline in urine has been shown to reflect very well the absorption of tetracycline (Tuomisto & Männistö, 1973; Neuvonen & Turakka, 1974).

As demonstrated in Figure 1 the absorption of both ^{59}Fe and tetracycline was decreased in all subjects when these compounds were ingested together compared to the absorption following their separate administration. The absorption of iron taken alone or simultaneously with tetracycline was 8.7 ± 1.4% (mean ± s.e. mean) and 4.4 ± 1.2% of the dose, respectively. Thus the absorption of iron decreased approximately to the half from the control values. The excretion of tetracycline in urine was 360 ± 37 mg and 91 ± 43 mg taken alone or simultaneously with iron, respectively. The decrease in absorption of both iron and tetracycline was statistically significant ($P < 0.005$, paired t-test).

The results of the present study clearly indicate the reciprocal inhibition of the absorption of simultaneously ingested ferrous sulphate and tetracycline. Tetracycline and iron in equimolar concentrations are known to form stabile chelates *in vitro* (Albert, 1953; Albert & Rees, 1956). This mechanism is obviously the basis for the inhibition of the tetracycline absorption by iron and explains also the reduced absorption of iron by tetracycline seen in the present study. The absorption of tetracycline is not significantly affected if the iron is administered more than 3 h apart from the tetracycline (Gothoni, Neuvonen, Mattila & Hackman, 1972). Furthermore, the interaction is less pronounced when the drugs are administered simultaneously if the iron is in the form of a slow-release preparation, which allows the tetracycline to be absorbed before the iron is liberated in the gut lumen (Mattila, Neuvonen, Gothoni &

Hackman, 1972). The same is also true for the inhibition of the iron absorption by tetracycline: the absorption of iron is not inhibited if the tetracycline is ingested at least 3 h apart from the iron or if a slow-release type of iron preparation is used. This explains also the findings of Greenberger (1973), who did not find any inhibition of the absorption of iron when the tetracycline was ingested 4 h before the iron.

It can be concluded that the simultaneous ingestion of iron and tetracycline is the premise for the interaction to occur and that the interaction results in a significantly reduced absorption of both these drugs.

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P.J. NEUVONEN

Department of Clinical Pharmacology, University of Helsinki, Finland

P.J. PENTIKÄINEN

Second Department of Medicine, University of Helsinki, Finland

G. GOTHONI

Research Laboratories of Medica Ltd, Helsinki, Finland

Received September 2, 1974

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