LONG-TERM LOW DOSE HALOPERIDOL TREATMENT IN RHEUMATOID PATIENTS: EFFECTS ON SERUM SULPHYDRYL LEVELS, TECHNETIUM INDEX, ESR, AND CLINICAL RESPONSE

Remittive drugs for rheumatoid arthritis (RA), such as hydroxychloroquine (Pickup, Dixon & Bird, 1980), aurothiomalate and D-penicillamine (Evans, 1977; Haataja, Nissila & Ruutsalo, 1978; Hall, 1980) levamisole (Hall & Gillan, 1979), and cyclophosphamide (Gutlan, 1979; Pickup *et al.*, 1980) have been found to induce in RA patients, during long-term treatment, a significant increase in serum sulphydryl (SH) total concentrations up to a return of these towards the normal range, accompanied by clinical improvement.

Low dose haloperidol, like the above drugs, has been shown to be able to induce in RA patients during 6 months of treatment a progressive and significant increase in serum protein SH levels, and a significant decrease in technetium index (Tc-index), erythrocyte sedimentation rate (ESR), and joint count (Grimaldi, 1980a; Grimaldi & Bergonzi, 1980). The studies described herein were designed to probe whether long-term haloperidol treatment induces a sustained increase in serum SH levels, and to evaluate whether the changes in serum SH concentrations correlate with the changes in objective indices of the disease activity, such as Tc-index, ESR, and joint count.

The subjects were 12 adult patients, who met the Committee of the American Association (1959) criteria for classification of definite RA. The mean age of the patients, nine females and three males, was 42 (range 25–71) years. All patients had active disease of at least 6 months duration, none had been administered antirheumatic remittive drugs before the start of scheduled treatment, and non-steroidal anti-inflammatory agents (NSAIAs) were withdrawn 1 week before beginning the haloperidol treatment. The subjects received all the information on the possible adverse effects of the drug and gave informed consent.

The patients were hospitalized at the start of the treatment, and were again hospitalized at 3 monthly intervals for radiographic, radioisotope, laboratory, and clinical assessment of disease activity. All patients were followed-up at weekly intervals, with appropriate clinical and laboratory studies at our rheumatologic outpatients service.

The haloperidol regimen was 1.5 mg/day orally.

Clinical assessment of disease activity was performed by measuring joint count, *i.e.* the number of joints tender, painful on passive movement, or those showing nonbony swelling (McCarty, 1979).

The determination of the serum SH total concentration and Tc-index were performed as previously described (Grimaldi, 1980a; Grimaldi & Bergonzi, 1980). Briefly, the protein SH levels in the sera were calculated spectrophotometrically, using 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) (Ellman, 1959). The amount of SH total concentrations in the tested sera is expressed in μmol/l. The normal values calculated in 100 healthy subjects, 50 females and 50 males, aged 21 to 79 years, were 338 ± 55 (s.d.) μmol/l (Grimaldi, 1980a). Since a significant negative correlation has been demonstrated between SH serum levels and age (Haataja, 1975), the RA patients' sera were matched for sex and age with the sera of healthy subjects.

The articular radioisotope uptake was expressed in percent ($\% \times 10^{-3}$) of the total activity, approximately 300 μCi of ^{99m}Tc-pertechnetate, injected in an ante-cubital vein. The mean value of eight count rates per subject (from second to fifth finger of each hand) represents the proximal interphalangeal joints Tc-index. In the healthy subjects this radioisotopic index is 2.3 ± 0.7 (s.d.) (Grimaldi & Bergonzi, 1980).

Numerical data for serum SH concentration, Tc-index, ESR, and joint count are shown as basal values, after twelve months treatment values, and as efficiency ratio (ER) which was calculated as follows:

$$ER = \frac{\text{basal value} - \text{post-treatment value}}{\text{basal value} - \text{mean normal value} \pm 1\ \text{s.d.}}$$

Serum prolactin levels were determined by a homologous radioimmunoassay for human prolactin (Sinha *et al.*, 1973).

The statistical studies were performed by Spearman correlation analysis, by Wilcoxon signed rank test, and by Mann-Whitney rank sum test, as appropriate.

Twelve months haloperidol treatment induced in all rheumatoid patients a highly significant increase in SH serum levels ($P < 0.01$), and a highly significant decrease in Tc-index, ESR, and joint count ($P < 0.01$; Table 1).

The SH serum concentrations returned towards the normal range, along with ESR and joint count in all 12 cases, and with Tc-index in nine cases. The results obtained in individual patients are shown in Figure 1.

Radiographic evaluation did not reveal substantial changes during treatment in any subject.

During haloperidol treatment the extrapyramidal effects were mild, more frequent in older patients, and were minimized by symptomatic drugs.

Serum prolactin levels were not elevated by the drug throughout the treatment period (basal levels,

Table 1 Effects of 12 months' haloperidol treatment (1.5 mg/day orally) on laboratory and clinical parameters of disease activity in twelve rheumatoid patients (mean ± s.d.)

Measurements	*Basal value*	*Post-treatment value*	*ER value*	P *value*
SH (μmol $^{-1}$l)	225 ± 41	349 ± 52	0.9 ± 0.1	<0.01
Tc-index*	4.5 ± 1.2	3.2 ± 0.8	0.9 ± 0.2	< 0.01
ESR (mm h^{-1})	37 ± 20	20 ± 7	0.9 ± 0.1	< 0.01
Joint count	12 ± 5	3 ± 1		< 0.01

* = % of the total injected activity

10.5 ± 1.7 (s.e. mean) ng/ml; at the end of the study, 11.1 ± 1.8 ng/ml).

A significant correlation was observed in ER as evaluated by SH serum levels *v* Tc-index ($r_s = 0.79$, $P < 0.01$).

This study extends previous findings (Grimaldi, 1980b; Grimaldi & Bergonzi, 1980), and shows that long-term low dose haloperidol treatment is able to induce after 12 months in rheumatoid patients a progressive increase of SH serum levels up to return of these towards the normal range along with clinical improvements.

As quoted in the introduction, the same ability has been found in the long-acting antirheumatic drugs hydroxychloquine (Pickup *et al.*, 1980), aurothiomalate and penicillamine (Evans, 1977; Haataja *et al.*, 1978; Hall & Gillan, 1979; Pickup *et al.*, 1980), levamisole (Hall & Gillan, 1979), and cyclophosphamide (Grimaldi, 1980a), irrespective of whether the drug molecule contains a thiol group.

Long-term haloperidol treatment, moreover, leads to a significant decrease of the Tc-index, which is thought to measure the effects of drug with specific activity in RA (Huskisson, Scott & Blame, 1976). After 12 months' treatment with haloperidol, indeed, a significant correlation was found in efficiency ratio (ER) as evaluated by serum SH levels *v* Tc-index.

The clinical improvement observed in haloperidol-treated patients thus seems to represent, as the ESR decrease, a specific effect of the drug on the process of the disease's activity.

The mode of action of this drug in RA is unknown. Possibly, the key to this question is the close platelet-haloperidol relationship. Haloperidol is known to bind to the blood platelet membrane (Boullin, Molineux & Roach, 1978) where it interacts with 5-hydroxytryptamine (5-HT). Indeed, haloperidol inhibits platelet 5-HT binding and uptake (Boullin *et al.*, 1978), and 5-HT-induced aggregation (Boullin & Glenton, 1978).

5-HT-haloperidol interactions in human platelets involve non-specific saturations by haloperidol of all platelet proteins (Boullin *et al.* 1978). This 'anesthetic' membrane-stabilizing effect on the platelets may possibly explain the true antirheumatic activity of the drug in RA (Grimaldi, 1980b; Grimaldi & Bergonzi, 1980).

Haloperidol might thus neutralize the immune-

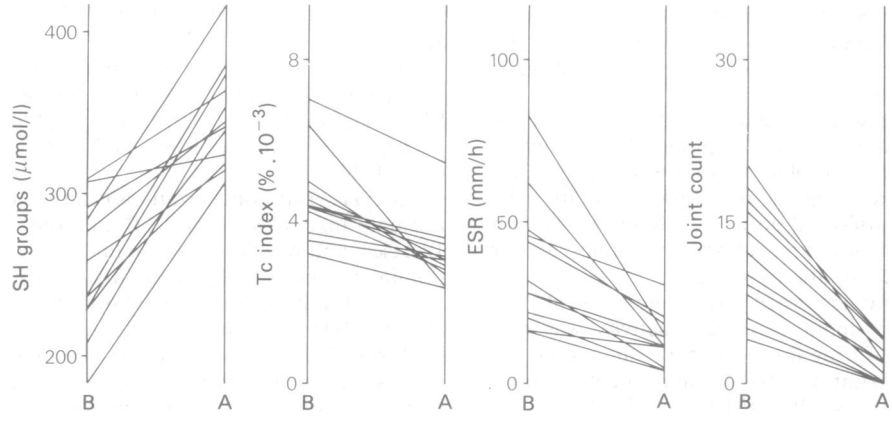

Figure 1 Effect of 12 months' haloperidol treatment on different laboratory and clinical parameters of disease activity in the individual rheumatoid patients. B before and A after 12 months' haloperidol.

related pathogenic activation of the platelets, leading to cessation of the exhaustive platelet 5-HT release (Crawford, 1969; Yeatts *et al.*, 1978).

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HYPOGLYCAEMIA INDUCED BY AZAPROPAZONE-TOLBUTAMIDE INTERACTION

The non-steroidal antirheumatic drug, azapropazone, is a recently marketed pyrazolidine derivative and accordingly analogous to phenylbutazone and oxyphenylbutazone. Serious and even fatal hypoglycaemic reactions have previously been reported when phenylbutazone has been given to tolbutamide-treated diabetics (Hansen & Christensen, 1977).

A 77-year old diabetic woman was admitted to the medical ward on June 23, 1980 with a diagnosis of cerebral thrombosis. She had an uncomplicated diabetes for 3 years, treated with diet and tolbutamide 500 mg twice daily. Concomitant treatment taken by the patient during this time was nitrazepam 5 mg in the night and occasionally diazepam 2 mg and a fixed combination of codeine 10 mg and acetylsalicylic acid 500 mg.

From June 18, azapropazone was administered in a dosage of 300 mg three times daily because of arthro-