

Comparison of phenytoin and gold as second line drugs in rheumatoid arthritis

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SUMMARY Phenytoin has known immunosuppressive properties, and a recent pilot study has indicated that it may have a second line effect in rheumatoid arthritis (RA). To evaluate this role 60 patients with active RA were randomly allocated to receive either oral phenytoin or intramuscular gold. The two treatment groups were comparable at the outset (Mann-Whitney U test). Twenty four patients completed 24 weeks of therapy in each group and no unexpected side effects were encountered. All variables except haemoglobin (Hb) improved significantly in the gold group while in the phenytoin group significant improvement was limited to articular index, erythrocyte sedimentation rate (ESR), and Hb. Between group comparison (Mann-Whitney) at week 24 showed a significant advantage of gold over phenytoin for pain score and morning stiffness. Thus phenytoin appears to exert a less potent second line effect than gold and is unusual in influencing laboratory indicators of disease activity more than clinical variables. This is likely to limit its usefulness as a second line drug in RA.

A recent pilot study carried out by Macfarlane *et al* has indicated that the antiepileptic drug phenytoin may have a second line effect in rheumatoid arthritis (RA).¹ This study was prompted by the fact that phenytoin has known immunosuppressive properties,² including the ability to reduce IgA levels selectively.³ The latter action is of particular significance as a large percentage of patients with chronic RA have raised serum IgA levels.⁴ The demonstration of second line properties in an established drug such as phenytoin would be of interest as its side effect profile is known from long experience in epilepsy. Phenytoin levels are readily available in most routine biochemical laboratories and their measurement would allow monitoring of compliance and should reduce the incidence of dose related side effects.

Patients and methods

Sixty patients with definite or classical RA who were inadequately controlled on first line therapy were randomly allocated to receive either oral phenytoin or intramuscular gold. The following groups were excluded from the study: epileptics, women of

childbearing years not receiving adequate contraceptives, and those with previous exposure to gold therapy. Phenytoin was started at 100 mg daily and increased by 50 mg every week until 'therapeutic' levels were obtained or side effects supervened. The therapeutic range for anticonvulsant use was employed (40-80 $\mu\text{mol/l}$). Free and total drug levels were measured and, in addition, the patients were asked a number of specific questions relating to changes in their mouth, gums, hair, vision, balance, and sleep patterns. An initial 10 mg test dose of gold was given intramuscularly followed by 50 mg weekly until a clinical response was seen or side effects developed. Gold therapy was considered to have failed if 20 weekly injections produced no benefit. Once benefit was achieved injections were given fortnightly.

At 0, 12, and 24 weeks a full blood count, platelets, and ESR were checked, while rheumatoid factor and antinuclear antibody were measured at 0 and 24 weeks. All patients were reviewed by the same metrologist at 0, 6, 12, and 24 weeks, who recorded pain using a 10 cm visual analogue scale, duration of morning stiffness, Ritchie articular index,⁵ and grip strength. The treatment given to any particular patient was not indicated to the metrologist.

All patients gave informed consent before entry into the study and were able to change to alternative

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Table 1 Comparison of data at weeks 12 and 24 with week 0 using a Wilcoxon matched pairs signed ranks test

	Phenytoin (n=24)			Gold (n=24)		
	0	12	24	0	12	24
Hb (g/l)	116	121 (NS)	122 (p=0.026)	119	114 (NS)	119 (NS)
Platelets $\times 10^{-9}/l$	394	403.5 (NS)	382.5 (p=0.018)	360.5	308.5 (p=0.001)	263 (p=0.001)
ESR (mm/h)	70	47 (p<0.001)	45 (p<0.001)	62	49 (p=0.014)	34 (p<0.001)
Pain (mm)	62	50 (NS)	50.5 (NS)	71.5	39 (p<0.001)	31 (p<0.001)
Morning stiffness (min)	60	45 (NS)	31 (NS)	110	30 (p=0.001)	8 (p<0.001)
Articular index	11.5	8.5 (NS)	8 (p=0.021)	14	6 (p<0.001)	7 (p<0.001)
Grip (mean) (mmHg)	84	73 (NS)	77.5 (NS)	84	82 (p=0.008)	90.5 (p=0.03)

therapy on request at any time during the study. Those continuing to receive treatment were requested to keep additional therapies constant as far as possible to minimise possible drug interactions.

Results

The median phenytoin level at week 12 was 39.5 $\mu\text{mol/l}$ (range 15–92 $\mu\text{mol/l}$) and was similar at week 24 at 42 $\mu\text{mol/l}$ (range 14–90 $\mu\text{mol/l}$). The median dose of phenytoin at week 12 was 350 mg/day (range 150–450 mg/day) and at week 24 was 367 mg/day (range 150–500 mg/day).

After 24 weeks 24 patients remained in each treatment group. The reasons for stopping treatment in the gold group were as follows: rash in two patients, lack of effect in one, and significant proteinuria in three. In the phenytoin group two patients stopped because of lack of effect and one each for the following reasons: rash, sleeping problems, and general lethargy with menstrual upset. One patient on phenytoin died of a systemic embolus during the study period. The treatment groups were comparable at the outset (Mann-Whitney). The results for the patients still receiving therapy are shown in Table 1. A significant improvement in all variables except Hb was shown in the gold group and in articular index, ESR, platelets, and Hb but not other variables in the phenytoin group. Comparison of gold and phenytoin at week 24 using a Mann-Whitney U test showed a significant advantage for gold in terms of platelets, pain score, and duration of morning stiffness.

Rheumatoid factor measurements were carried out in two laboratories using a Rose-Waaler and an enzyme linked immunosorbent assay (ELISA) tech-

nique. Using the Rose-Waaler method in the phenytoin patients (n=12) the median rheumatoid factor remained static from week 0 to week 24, whereas in the gold patients (n=12) the median rheumatoid factor changed from 1/256 to 1/32 (p=0.012; Wilcoxon matched pairs signed ranks test). Similarly, the median rheumatoid factor measured by the ELISA technique in the phenytoin patients (n=9) changed from 8800 to 5600 units/ml (not significant), whereas in the gold group (n=9) the change was from 4650 to 1800 units/ml (p<0.02; Wilcoxon matched pairs signed ranks test).

There was a wide range of phenytoin levels at week 24 (14–90 $\mu\text{mol/l}$). We therefore compared the degree of change in clinical and laboratory parameters in those patients with a level less than the median value at week 24 (42 $\mu\text{mol/l}$) with those who attained a level greater than the median. There was no significant difference between the groups.

Discussion

This study was designed to assess the place of phenytoin as a second line agent in rheumatoid arthritis. No unexpected toxicity was encountered with either gold or phenytoin. We arbitrarily chose a therapeutic level consistent with that used in patients treated with phenytoin for seizures. These levels were satisfactorily achieved at weeks 12 and 24 in most cases.

The expected clinical and laboratory response was seen in the gold treatment group. There was, however, no evidence of a second line effect in the phenytoin group in terms of symptom control, though significant changes were shown in the Ritchie articular index after 24 weeks' treatment.

Nevertheless, there did appear to be a laboratory response to phenytoin in that the haemoglobin rose and the ESR and platelets fell.

The discordant clinical and laboratory effects of phenytoin are difficult to explain. It is conceivable that this drug selectively offers control of laboratory parameters; if so it is unique in the group of second line drugs. If control of ESR within the normal range prevents the progression of radiological erosion this may make phenytoin a useful additional treatment, particularly in patients with progressive destructive disease but relatively few symptoms. Our experience, however, with other second line drugs has not confirmed an association between change in ESR and radiological progression.⁷

An alternative explanation for the dissociation in the clinical and laboratory response may be an alteration in hepatic metabolism, and it is possible that phenytoin influences hepatic synthesis of acute phase reactants and proteins such as transferrin to favour a laboratory response in RA.

Geaney *et al* have described an interaction between azapropazone and phenytoin,⁸ and it may be that there is an interaction between phenytoin and other non-steroidal anti-inflammatory drugs. This may lead to increased excretion of these drugs, suppressing their effects, and hence producing a less obvious clinical than laboratory response. Nevertheless, clinically important interactions between phenytoin and other drugs appear to be the exception rather than the rule.

In practice it is likely to prove difficult to persuade patients to comply with therapy if they do not

perceive benefit. Thus patient acceptance is likely to limit the possible long term benefits of phenytoin in rheumatoid arthritis. In addition, greater efficacy was achieved with gold than with phenytoin, indicating that phenytoin is unlikely to become a first choice second line agent.

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