

No significant effects of sodium aurothiomalate on haem metabolism and mixed function oxygenase activity in patients with rheumatoid arthritis

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Rheumatoid arthritis, gold, haem metabolism, cytochrome P-450, antipyrine clearance, hepatic drug metabolism.

ABSTRACT

Objective.

Animal studies suggest that gold compounds impair haem synthesis and increase haem degradation and, as a result, reduce activity of the hepatic haemoproteins cytochromes P-450. The aim of this study was to investigate whether intramuscular gold exerts similar effects in patients with rheumatoid arthritis (RA).

Methods.

Urinary porphyrin and precursor excretion, erythrocyte protoporphyrin, and antipyrine clearance, were measured in 6 patients with RA before and 10 weeks after commencement of intramuscular gold.

Results.

Parameters of haem metabolism were unaffected by gold. While antipyrine clearance was not statistically changed after gold treatment, in 3 of the patients there was an average decrease in antipyrine clearance of 23%.

Conclusion.

Further studies examining RA patients at different time points are required to investigate further the possibility of reduced hepatic drug metabolising activity during prolonged treatment with gold.

Introduction

Patients with rheumatoid arthritis (RA) are often prescribed a number of different drugs, putting them at risk of drug interactions, although these may be subtle and not always clinically recognised. We set out to investigate whether gold compounds reduce activity of the hepatic haemoproteins cytochrome P-450 in patients with RA in the same way as has been shown in laboratory animals. If so, this might affect the ability of patients with RA on gold to metabolise certain drugs (for example, several NSAIDs) which are handled by the mixed function oxygenase system. Cytochromes P-450 form the terminal component of this system.

Our interest in this area was prompted by the suggestion from animal studies that gold compounds impair haem biosynthesis (by reducing activity of aminolaevulinic acid (ALA) dehydratase and of ferrochelatase, both of which are important in haem biosynthesis), and increase the activity of haem oxygenase,

which catalyses the breakdown of haem to biliverdin (1). Reduced biosynthesis and increased degradation of haem could result in reduced activity of the hepatic haemoproteins cytochrome P-450, and these changes have been demonstrated in laboratory animals after both gold sodium thiomalate and auranofin (1-3).

Patients and methods

Six patients with seropositive RA (1 male, 5 female) were studied before and ten weeks after commencing intramuscular gold (sodium aurothiomalate). None had previously been prescribed gold. Their median age was 57 years (range 28 - 64 years), and all had active disease on recruitment into the study. The total dosage of sodium aurothiomalate administered to each patient was either 460 mg or 510 mg. The study was approved by the Salford Research Ethics Committee.

While all patients were on other drugs in addition to the gold, in most cases these remained unchanged during the study period. One patient commenced dothiepin and a diuretic during the study period and two patients commenced iron supplements. With respect to local steroid injections during the study period, two patients received these within the week following entry into the study and a third patient had two local steroid injections later on in the study period (one two days prior to her second study). With respect to NSAIDs, four of the six patients were on diclofenac sodium, one was on naproxen, and one patient was not on an NSAID.

Twenty-four hour urinary porphyrins and the porphyrin precursors ALA and porphobilinogen (PBG), erythrocyte protoporphyrin, and antipyrine kinetics were measured prior to and ten weeks after the commencement of gold injections. Urinary porphyrins were measured by high-performance liquid chromatography (HPLC) (4) and urinary ALA and PBG by the method of Mauzerall and Granick (5). Urinary ALA would be expected to rise if ALA dehydratase was reduced. Erythrocyte protoporphyrin was measured as described by Piomelli (6): erythrocyte protoporphyrin might rise if ferrochelatase activity was reduced.

Table I. Urinary porphyrin and precursor excretion, erythrocyte protoporphyrin and antipyrine clearance in six patients with RA before and after intramuscular gold. Values presented are the medians (range).

	Pre-gold		10 weeks' treatment		Reference range
Amino-laevulinic acid* ($\mu\text{mol}/24\text{ hr}$)	16	(9 - 21)	11	(7 - 16)	< 40
Porphobilinogen* ($\mu\text{mol}/24\text{ hr}$)	3.5	(2 - 14)	2.5	(2 - 5)	< 16
Uroporphyrin* (nmol/24 hr)	14	(10 - 25)	19	(10 - 34)	< 40
Coproporphyrin* (nmol/24 hr)	80	(20 - 210)	139	(0 - 185)	< 370
Erythrocyte protoporphyrin ⁺ ($\mu\text{mol}/\text{l RBC}$)	0.93	(0.32 - 1.02)	1.10	(0.32 - 1.40)	< 2
Antipyrine clearance (ml/hr)	490	(271 - 1190)	438	(327 - 796)	-

* 24 hr urinary excretion; ⁺ 5 patients

Antipyrine kinetics were measured over a 48-hour period. Antipyrine clearance is an index of the oxidative function of cytochromes P-450. A 600 mg oral dose of antipyrine was given at around 0900 h after an overnight fast and concentrations measured in saliva by HPLC (7) at 3, 5, 8, 12, 24, 27, 32 and 48 hours. Results before and after gold treatment were compared using the Wilcoxon's paired samples signed rank test.

Results

The results are shown in Table I and Figure 1. In none of the patients was there any abnormality in any of the parameters of haem metabolism studied, and these parameters were unaffected by gold. While antipyrine clearance was not statistically changed after gold treatment, in 3 of the patients there was an average decrease of antipyrine clearance of 23%.

Discussion

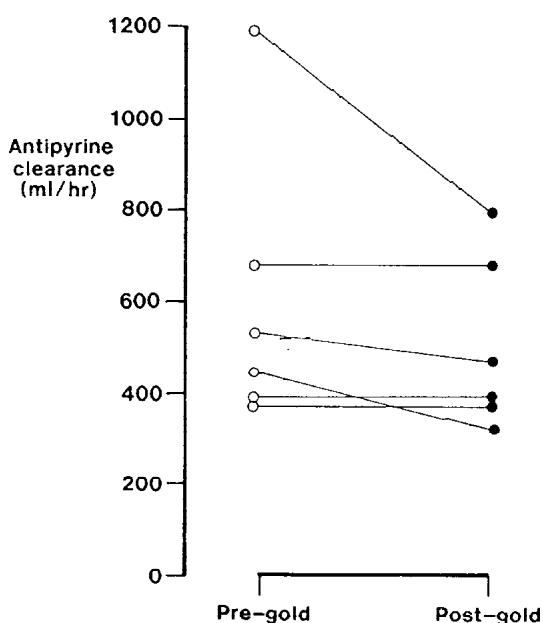
In this small study, ten weeks of gold administration caused no alterations in haem metabolism as assessed by measurement of urinary porphyrins and precursors and erythrocyte protoporphyrin. However, these techniques may be relatively insensitive in detecting abnormalities in haem metabolism: the studies examining effects of gold on enzymes of haem metabolism in laboratory animals measured enzymic activity in liver and kidney.

While there were no statistically significant changes in cytochrome P-450 activity as measured by antipyrine kinetics, nonetheless antipyrine clearance did fall in three patients, which is suggestive of reduced cytochrome P-450 activity in this subgroup. Cytochromes P-450 are the major group of hepatic haemoproteins, forming the terminal compo-

nent of the mixed function oxygenase system. They are all-important in the metabolism of many drugs. Any decrease in the activity of cytochromes P-450 could therefore have important clinical implications: impaired drug metabolism could lead to an increase in toxicity. Many patients with RA are prescribed gold preparations, and often drugs metabolised by cytochrome P-450 (for example several of the NSAIDs) are given concomitantly. Although the experimental work by Eiseman and Alvares demonstrated acute rather than chronic effects of gold on haem metabolism and on cytochrome P-450 (1), the dose and time dependency of changes in haem metabolism and cytochrome P-450 as a result of gold administration are complex and may vary between tissues (3). Therefore it may be that in our pilot study, had the gold been administered for a longer period, then significant falls in antipyrine clearance might have been observed. This is an area which needs further study, examining patients before and at different time points during prolonged treatment with gold.

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**Fig. 1.** Antipyrine clearance in 6 patients with RA before and ten weeks after commencing intramuscular gold.