Patterns of urinary excretion of gold in patients with rheumatoid arthritis undergoing chrysotherapy

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SUMMARY Thirty patients receiving gold therapy for rheumatoid arthritis (RA) were studied for the urinary excretion of gold. Statistical analysis of all the urine specimens passed over a period of four days by each patient showed that a definite rhythm of gold excretion exists for each patient which is possibly related to water excretion but not to creatinine excretion. The study indicates possible reasons for the inability of earlier workers to relate gold excretion to the general body gold status of patients and suggests that as the study of 24 hour excretions of gold may be an insensitive marker of gold excretion, closer examination of individual patient rhythms of gold excretion could possibly provide a more useful method of analysis.

Key words: circadian rhythms, aurothiomalate.

The management of rheumatoid arthritis (RA) by gold therapy is based on more than 50 years’ experience. During this time successful management has been plagued by the inability to relate consistently any easily measurable parameter to the potential efficacy or toxicity of the treatment.

One area of investigation has been the relation of serum gold to urinary gold. The findings of the various investigators, however, have been in the main, contradictory. Freyberg et al found no correlation between serum and urine gold levels,1 and nor did Lawrence.2 Smith et al found that a poor therapeutic effect was related to a high urinary gold excretion and toxic reactions to a low excretion,3 but Krusius et al4 and Billings et al5 concluded that although serum gold levels correlated with therapeutic efficacy, urine levels did not.

It is evident, however, that the types of urine specimens studied and the methods of reporting gold levels have differed in various studies. For example, Krusius et al4 and Arden-Jones et al6 reported excretion of gold in milligrams per 24 hours, whereas Billings et al reported the excretion of gold in random urine specimens as micrograms per gram of creatinine.5 The aim of this study is to investigate the possibility of the existence of circadian periodicity in the excretion of gold and to compare this with the endogenous rhythms of water and creatinine excretion. Clearly, the existence of a rhythm of gold excretion would cause variations in daily random urine gold levels. Furthermore, should the rhythms be different from the creatinine rhythms of excretion then the calculation of results as excretion in micrograms per gram of creatinine would compound inconsistency in results.

Patients and methods

Thirty patients receiving gold therapy for RA diagnosed according to the American Rheumatism Association7 criteria were admitted to the study. All patients were receiving a regular fortnightly or monthly stabilised dose of sodium aurothiomalate and had a disease duration of between six months and five years. Twenty one subjects were female and nine were male, and all were in an age range of 16–65 years. Patients receiving corticosteroids were excluded from the study. Five were inpatients at the Nottingham City Hospital and twenty five were outpatients.

The patients measured the volumes of all urine specimens passed over a 24 hour period using collecting jugs and measuring cylinders which were provided and placed aliquots of each specimen into labelled bottles. The volumes were recorded on forms which were supplied, together with the time of micturition. The procedure was carried out for a minimum period of four days.8
**ANALYSIS**

All urine specimens were analysed for gold content by atomic absorption spectroscopy. Creatinine assays were performed on each specimen using an Instrumentation Laboratory 508 analyser, which adopts the traditional Jaffe alkaline picrate method. From the results, both gold and creatinine excretion rates were calculated. The excretion rates for water were also calculated.

**DATA ANALYSIS**

The data obtained from the study were analysed as follows: (a) histograms were plotted for each patient study period of excretion rates (gold, creatinine, and water) against time; (b) results from each patient were analysed for periodicity by the sine wave technique developed by Fort and Mills; (c) Pearson correlations were calculated for gold excretion against water excretion and for gold excretion against creatinine excretion both for the patient group and for the individual patients.

**Results**

**HISTOGRAM ANALYSIS**

**Gold**

The individual histograms of gold excretion for 28 of the 30 patients studied described regular patterns of excretion throughout the four day study. Twenty four patients showed biphasic patterns, four monophasic, and two triphasic patterns of excretion.

Patient No 1 shown in Fig. 1 demonstrates a biphasic pattern with its peaks at 03-02 and 16-12 hours.

**Water**

The histograms for water excretion showed peaks and troughs similar to those for gold excretion for the same days when analysed by eye. Patient No 1 (shown in Fig. 2) demonstrates a biphasic pattern with peaks at 05-00 and 16-25 hours.

**Creatinine**

Although individual patterns of creatinine excretion were dissimilar to those of gold and water excretion.

![Fig. 1](image-url) *The histograms for patient No 1 show regular biphasic patterns of gold excretion.*

![Fig. 2](image-url) *The histograms for patient No 1 show regular biphasic patterns of water excretion.*

![Fig. 3](image-url) *The histograms for patient No 1 show biphasic patterns of creatinine excretion. These patterns are dissimilar to those of gold and water excretion.*
were evident, thoughout the group only six patients showed excretion rates and times similar to those of gold and water. Patient No 1 shown in Fig. 3 demonstrates biphasic patterns of excretion, but these are dissimilar to the gold and water excretion patterns for this patient. The peaks are at 10-10 and 19-58 hours.

**SINE WAVE ANALYSIS**

Each of 28 patients showed individual statistically significant circadian rhythmicity of urinary gold excretion. The same subjects demonstrated rhythmicity for water and urinary creatinine excretion. It can be seen from the results that although in individual subjects the acrophases for gold and water excretion were similar, this occurred in only six instances for gold and creatinine excretion. Table 1 shows six examples of patients with similar individual acrophases for gold and water excretion, and one example of a patient with similar acrophases for gold, water, and creatinine excretion.

In the two instances where no regular patterns of excretion were detected one patient commenced steroid medication during the study, and the other had a very high, random (including nocturnal) intake of tea, which has known diuretic properties.

**CORRELATION RESULTS**

From the results of a group correlation between gold excretion and water excretion it is evident that correlation was poor (r=0-32, p=0-10, n=140). Individual patient correlation plots, however, showed good correlation, with all correlation coefficients greater than 0-85 and with p values less than 0-05 (see Fig. 4). There was no apparent correlation between the patient group creatinine excretion rates and water excretion rates (r<0-25, p>0-1), and also bad correlation for 22 patients when individually plotted (r<0-2, p>0-1). Six patients showed good correlation between creatinine and gold excretion rates.

**Discussion**

The histogram and sine wave analysis of results indicates that statistically significant individual patient rhythms exist for the urinary excretion of gold. These are similar to those of water excretion in all cases, but similar to creatinine excretion in a minority (six out of 28) of the subjects studied. Correlation studies show that the excretion of gold is possibly related to the excretion of water by the

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**Table 1  Sine wave analysis results for gold, water, and creatinine excretion**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>10^2 * M* (µmol/min)</th>
<th>10^2 * A* (µmol/min)</th>
<th>Acr* (h)</th>
<th>Value</th>
<th>M (ml/min)</th>
<th>A (ml/min)</th>
<th>Acr (h)</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.85</td>
<td>0.46</td>
<td>16-12</td>
<td>0-03</td>
<td>1-42</td>
<td>0.74</td>
<td>16-25</td>
<td>0-04</td>
</tr>
<tr>
<td>2</td>
<td>0.82</td>
<td>0.71</td>
<td>20-58</td>
<td>0-05</td>
<td>1-54</td>
<td>0.89</td>
<td>20-32</td>
<td>0-05</td>
</tr>
<tr>
<td>3</td>
<td>0.95</td>
<td>0.35</td>
<td>16-53</td>
<td>0-04</td>
<td>1-69</td>
<td>0.76</td>
<td>16-04</td>
<td>0-03</td>
</tr>
<tr>
<td>4</td>
<td>1.31</td>
<td>0.42</td>
<td>17-13</td>
<td>0-03</td>
<td>2-14</td>
<td>1.04</td>
<td>17-01</td>
<td>0-02</td>
</tr>
<tr>
<td>5</td>
<td>1.45</td>
<td>0.66</td>
<td>16-18</td>
<td>0-05</td>
<td>1-92</td>
<td>0.94</td>
<td>16-52</td>
<td>0-05</td>
</tr>
<tr>
<td>6</td>
<td>1.56</td>
<td>0.86</td>
<td>01-29</td>
<td>0-03</td>
<td>1-98</td>
<td>0.92</td>
<td>2-00</td>
<td>0-03</td>
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<tr>
<td>7</td>
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<td>0.95</td>
<td>23-24</td>
<td>0-05</td>
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<td>1.42</td>
<td>23-58</td>
<td>0-05</td>
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<tr>
<td>8</td>
<td>1-20</td>
<td>1.04</td>
<td>22-30</td>
<td>0-05</td>
<td>3-01</td>
<td>1-01</td>
<td>23-30</td>
<td>0-06</td>
</tr>
</tbody>
</table>

*M = mesor; A = amplitude; Acr = acrophase.*
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kidney, but not related to the excretion of creatinine.

This study suggests possible reasons for the disparities achieved by earlier workers in attempting to relate urinary excretion of gold to the body status using random urine specimens and random specimens corrected for creatinine content. Clearly, random urine specimens from each subject will have different gold levels depending upon the times of collection. It is likely that correcting random urine gold levels for creatinine content will compound inconsistencies in results found between random specimens owing to the existence of creatinine excretory rhythms which are often different from those of gold. If efficacy or toxicity of treatment is reflected in changes in gold excretion it is possible that these alterations are likely to be more readily detected by observation of changes in the excretory rhythms or in the excretory rates (μmol/min) rather than in changes in total 24 hour excretion. Measurement of total 24 hour gold excretion could mask any subtle alterations in excretion rates occurring at different times of the day.

References
8 Heath M J. The composition of the urine at different times of day and night in patients who have undergone renal transplantation. University of Nottingham, 1981; 16-19. (M Phil.)