NEW URICOSURIC AGENT IN THE TREATMENT OF GOUT
para-CARBOXYBENZENESULPHA-DIETHYLAMIDE (URELIM)

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AND
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Several uricosuric drugs are now available for the long-term management of gout, the principal being aspirin, probenecid (Benemid), and sulphinpyrazone (Anturan). Recently two further drugs, Zoxazolamine (Flexin) and p-carboxybenzenesulpha-diethylamide (Urelim), have been introduced. Reed, Feichtmeier, and Willett (1958) commented on the uricosuric properties of Zoxazolamine, and drew attention to the numerous, albeit rarely serious, side-effects. To be effective in the treatment of gout, aspirin must be administered in large doses which may not be tolerated or may provoke toxic reactions. Probenecid is known to cause severe gastritis and rashes in some patients, and may occasionally cause hypersensitivity reactions. Sulphinpyrazone has been shown to carry the same risk of peptic ulceration as phenylbutazone in the rat (Domenjoz, 1960), and it is not unlikely that some of the other side-effects encountered with phenylbutazone may also occur with sulphinpyrazone, e.g. rashes and occasional blood dyscrasias.

The only published information concerning Urelim in the treatment of gout is a mention by Kersley, Cook, and Tovey (1958) of a comparison of this drug, then known as “Longacid”, with sulphinpyrazone. They found that a dosage of 1 to 2 g. daily of Urelim resulted in an increased output of uric acid, but in only three out of eleven patients tested was the uricosuric effect equal to that obtained from 400 mg. sulphinpyrazone daily. Four patients reported drowsiness while taking Urelim, but no other side-effects were noted.

The present report is concerned with an evaluation of Urelim therapy in six patients studied in detail. Five of them suffered from primary gout and one had gout secondary to polycythaemia vera. Information was sought concerning the value of Urelim as a uricosuric agent, its dosage and optimum method of administration, effect on the serum uric acid level and the course of the illness, and any possible toxic or undesirable side-effects. The effect of aspirin given in combination with Urelim was also investigated. Only one patient was admitted to hospital during the period of investigation.

All patients were allowed a normal diet with adequate fluids, excluding only foods with a high purine content. All urine passed during the period of observation was collected in 24-hr samples, and the volume, uric acid, and creatinine contents were measured. The determination of volume and creatinine served as a check on the efficiency of collection. Serum uric acid was determined by a modification of Benedict’s method, and blood urea and creatinine levels were also estimated at frequent intervals. Haemoglobin and white blood cell counts were also determined before and during the treatment periods. Special care was taken to ensure that no drugs with uricosuric effect, other than those prescribed, were administered during these studies. To simplify the presentation of results only mean values of uric acid excretion and serum uric acid are given for the various control and treatment periods. A minimum of 3 days’ urine collection was required for a control period (i.e. without any uricosuric drug) and for the comparison of different
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Drugs. When a patient changed from one uricosuric agent to another, urine collections continued without interruption, but the results in the 24-hr specimen immediately after the change-over were omitted from the calculations of the mean uric acid excretion. Urelim was supplied in the form of white insoluble tablets without any characteristic taste, containing 500 mg. p-carboxybenzenesulfaphenylacetamide.

**Case Reports**

**Case 1**, a male student aged 22 years, who had a history of asthma and duodenal ulcer, developed acute gout on July 4, 1960, and successive serum uric acid levels were 8.5, 8.4, and 9.5 mg. per 100 ml., before he was started on Urelim. The subsequent findings and clinical course are shown in Table I. The acute attack of gout which supervened after Urelim and probenecid therapy was relieved by a short course of phenylbutazone.

**Case 2**, a retired steel worker aged 68 years, had a history of recurrent attacks of gouty arthritis for 10 years. The last major attack was in May, 1960, and after treatment with colchicine and probenecid he was given delta-butazolidin. This was discontinued on July 20, 1960, and after a control period of 5 days without any treatment, the patient started Urelim therapy. His gout remained quiescent throughout the period of investigation. The findings are summarized in Table II.

**Case 3**, a retired shopkeeper aged 66 years, had suffered from polycythemia vera for 12 years and had developed gout in several joints in his hands and feet since 1956. He had been given colchicine tablets and probenecid intermittently since then and had taken probenecid 2 g. daily for 3 months before having a short trial of Urelim therapy. This patient also suffered from the mild residual effects of a left cerebral thrombosis, and observations were limited as he was treated at home. The findings are summarized in Table III.

### Table I

**OBSERVATIONS IN CASE 1**

<table>
<thead>
<tr>
<th>Medication . . . .</th>
<th>Control</th>
<th>Urelim 500 mg.</th>
<th>Urelim 1 g.</th>
<th>Benemid 1 g.</th>
<th>Benemid 1 g. + Urelim 1 g.</th>
<th>Urelim 1 g.</th>
<th>Control</th>
<th>Urelim 1.5 g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days) . .</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>17</td>
<td>5</td>
<td>20</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Mean Serum Uric Acid (mg./100 ml.) . .</td>
<td>9.5</td>
<td>9.6</td>
<td>10.7</td>
<td>6.3</td>
<td>5.3</td>
<td>—</td>
<td>12.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Mean 24-hr Uric Acid Output (mg.) . .</td>
<td>672</td>
<td>861</td>
<td>857</td>
<td>1,529</td>
<td>43</td>
<td>778</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clinical Course . .</td>
<td>Mild gout arthritis</td>
<td>Symptom free</td>
<td>No signs of gout</td>
<td>Mild dyspepsia</td>
<td>Increased dyspepsia</td>
<td>No dyspepsia but acute asthma and gout*</td>
<td>Symptom free</td>
<td>Symptom free</td>
</tr>
</tbody>
</table>

* Acute gout relieved by phenylbutazone 600 mg. for 3 days.

### Table II

**OBSERVATIONS IN CASE 2**

<table>
<thead>
<tr>
<th>Medication . . . .</th>
<th>Control</th>
<th>Urelim 1 g.</th>
<th>Urelim 2 g.</th>
<th>Sulphinpyrazone 300 mg.</th>
<th>Urelim 2 g. + Sulphinpyrazone 300 mg.</th>
<th>Urelim 2 g.</th>
<th>Urelim 1 g.</th>
<th>Urelim 1 g. + Aspirin 4·8 g.</th>
<th>Urelim 2 g. + Aspirin 4·8 g.</th>
<th>Urelim 3 g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days) . .</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>25</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mean Serum Uric Acid (mg./100 ml.) . .</td>
<td>8·4</td>
<td>7·1</td>
<td>5·4</td>
<td>4·8</td>
<td>5·8</td>
<td>8·7</td>
<td>7·5</td>
<td>10·4</td>
<td>9·0</td>
<td>8·6</td>
</tr>
<tr>
<td>Mean 24-hr Uric Acid Output (mg.) . .</td>
<td>179</td>
<td>238</td>
<td>271</td>
<td>20</td>
<td>164</td>
<td>190</td>
<td>225</td>
<td>365</td>
<td>280</td>
<td>235</td>
</tr>
</tbody>
</table>
Case 4, a bus driver aged 47 years, had suffered from recurrent attacks of gouty arthritis in his knees and feet for 13 years. He had not obtained relief from previous aspirin therapy nor from probenecid. Sulphinpyrazone (Anturan) had been effective and he had taken 400 mg. daily for nearly 1 year, the only side-effects being recurrent mild renal haemorrhages without evidence of nephrolithiasis. After a control period of observation while on sulphinpyrazone therapy, the patient started Urelim on August 12, 1960. The subsequent findings are summarized in Table IV.

<table>
<thead>
<tr>
<th>Medication</th>
<th></th>
<th>Sulphinpyrazone 400 mg.</th>
<th>Urelim 2 g.</th>
<th>Sulphinpyrazone 400 mg. + Urelim 2 g.</th>
<th>Urelim 1-5 g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Nearly one year</td>
<td>5 days</td>
<td>6 days</td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Mean Serum Uric Acid (mg./100 ml.)</td>
<td>6·3</td>
<td>6·6</td>
<td>4·0</td>
<td>6·8</td>
<td></td>
</tr>
<tr>
<td>Mean 24-hr Uric Acid Output (mg.)</td>
<td>672</td>
<td>440</td>
<td>183</td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

Case 5, a commercial traveller aged 54 years, had suffered from recurrent attacks of gout for 19 years, and had received intermittent treatment with colchicine and probenecid. He was admitted to hospital on July 1, 1960, because of an acute attack of gout and this responded partially to treatment with colchicine. After a control period, he started Urelim therapy on July 22, 1960. He sustained an acute exacerbation of gouty arthritis after 12 days of Urelim therapy, but this responded to phenylbutazone 600 mg. for 3 days. Further findings and the effect of 10 days combined treatment with aspirin and Urelim are shown in Table V.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Control</th>
<th>Urelim 1 g.</th>
<th>Urelim 1 g. + Phenylbutazone 600 mg.</th>
<th>Urelim 1-5 g.</th>
<th>Urelim 2 g.</th>
<th>Urelim 1 g. + Aspirin 4-8 g.</th>
<th>Urelim 2 g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days)</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Mean Serum Uric Acid (mg./100 ml.)</td>
<td>6·5</td>
<td>5·4</td>
<td>6·7</td>
<td>5·0</td>
<td>4·0</td>
<td>8·8</td>
<td>6·5</td>
</tr>
<tr>
<td>Mean 24-hr Uric Acid Output (mg.)</td>
<td>317</td>
<td>462</td>
<td>633</td>
<td>372</td>
<td>—</td>
<td>418</td>
<td>—</td>
</tr>
<tr>
<td>Signs of Gout</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Case 6, a housewife aged 72 years, had suffered from chronic tophaceous gout for 18 years. She had mild continuous joint pains in her hands and feet and some of the tophi had ulcerated. She could not tolerate aspirin in large dosage and previous therapy with probenecid had provoked violent hypersensitivity reactions on several occasions. A control serum uric acid level was 9·8 mg. on September 24, 1960, and she then started Urelim therapy, 0·5 g. daily for 7 days increasing to 1 g. daily for 10 days. Tabs. colchicine B.P. gr. 1/120 were given concurrently and she was found to be able to take Urelim with no side-effects.

Discussion

In three patients (Cases 1, 2, and 5) it was possible to obtain a direct measurement of the uricosuric effect of Urelim after a control period.

In Case 1, the uric acid output was raised by 28 per cent. during treatment with Urelim 0·5 g. daily and there was no greater output when the dosage was increased to 1 g. daily (Table I).

Case 2 showed an increase of 33 per cent. uric acid output on 1 g. Urelim daily and 51 per cent. when the dosage was raised to 2 g. (Table II).

Case 5 showed an increased uric acid output of 46 per cent. when given 1 g. Urelim daily (Table V). These results support the claim that Urelim is a potent uricosuric agent, and indicate that 1 g. daily will increase the uric acid output by as much as 28 to 46 per cent. Increasing the Urelim dosage (from 0·5 to 1 g. daily) did not result in an increase in uric acid excretion in Case 1; this was probably due to the fact that this patient took the daily dosage of two tablets together. This induced slight and transient drowsiness which later ceased when he took the drug in divided doses. It seems advisable that the Urelim dosage should be distributed throughout the day, in keeping with the recommended method of administration of other uricosuric agents, e.g. probenecid (Brochner-Mortensen, 1958) and sulphinpyrazone (Kersley and others, 1958).

Urelim was well tolerated by all the patients in this series and during the short periods of treatment, ranging from 9 to 72 days, no serious side-effects occurred. As already mentioned, one patient (Case 1) noted slight and transient drowsiness about 4 hours after taking 1 g. Urelim, but he has sub-
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sequently taken 500 mg. three times daily without any recurrence of this symptom. Case 4 had a mild urticarial rash while taking 2 g. Urelim daily, but this subsided while he continued to take this drug and it has not recurred after a further 37 days of treatment with 1·5 g. daily. This patient had previously been subject to urticaria.

Even in this small series, three of the six patients were not able to tolerate other uricosuric drugs and Urelim assumed an important place in treatment. Case 1 could not take aspirin because of a duodenal ulcer, probenecid provoked dyspepsia, and sulphinpyrazone was not advocated because of gastro-intestinal risks, but Urelim has been administered for 37 days with no dyspeptic symptoms. Case 4 could not tolerate aspirin, probenecid had not helped him previously, and sulphinpyrazone had provoked haematuria, but he has taken Urelim for 60 days with no upset other than the mild urticarial rash which was not necessarily due to Urelim. Case 6 had previously experienced severe hypersensitivity reactions, with malaise, rash, and vomiting, on the several occasions on which she had attempted to take probenecid, and large doses of aspirin were not tolerated, but she was able to take 1 g. Urelim daily without upset. No significant alterations in white blood cell counts were noted during the periods of observation in these six patients.

The short-term effects of a uricosuric agent are not so evident in changes in the serum uric acid level as in the urinary uric acid output, and with small doses of aspirin the serum uric acid level may rise even though the urinary uric acid excretion rises (Brøchner-Mortensen, 1958). There were four patients in our series in whom the effect of Urelim on the serum uric acid level was observed. In Case 1 the serum uric acid level rose from 9·5 to 9·6 mg./100 ml. on 0·5 g. Urelim daily, and from 9·6 to 10·7 mg./100 ml. on 1 g. Urelim daily, even though the urinary uric acid output had increased (Table I). Case 2 showed a fall in the serum uric acid level from 8·4 to 7·1 mg./100 ml. on 1 g. Urelim daily, and from 7·1 to 5·4 mg./100 ml. on 2 g. Urelim daily, this being associated with successive increases in urinary uric acid output (Table II). Case 5 also showed a steady fall from 6·7 to 4·0 mg./100 ml. on 1 g. Urelim (Table V) and this was correlated with increased urinary uric acid output. Case 6 received only a small dosage of 0·5 g. Urelim daily for 1 week increasing to 1 g. daily for 10 days, and the serum uric acid level fell from 9·8 to 8·8 mg./100 ml.

From present data it can be said that Urelim is an effective uricosuric drug. The question of the potency of Urelim milligram for milligram in comparison with probenecid and sulphinpyrazone is of little moment. The important points concerning a drug are whether it is effective and whether it can be taken without undesirable side-effects, and short-term studies suggest that Urelim meets these requirements.

In view of the known inhibiting effect of salicylate upon the uricosuric actions of probenecid (Brøchner-Mortensen, 1958) and sulphinpyrazone (Ogryzlo and Harrison, 1957), and in view of the widespread use of analgesics containing aspirin, it seemed advisable to investigate the influence of aspirin upon the uricosuric effect of Urelim. Aspirin in a dosage of 4·8 g. (72 gr.) daily was administered to Cases 2 and 5. In both patients the serum uric acid levels rose quickly and appreciably, but there was little effect on the urinary uric acid output. These findings suggest that patients receiving Urelim should be advised to avoid analgesics containing aspirin.

We have studied the effect of some of these drugs in combination and in sequence. There was a dramatic fall in urinary uric acid output when a patient was transferred immediately from 2 g. Urelim to 300 mg. sulphinpyrazone daily (Table II). The combinations of Urelim and probenecid (Table I), and of Urelim and sulphinpyrazone (Table IV) led to marked reduction in urinary uric acid output. These preliminary findings could be of importance in the treatment of gout, and further studies are in progress.

It is generally sound advice for patients receiving uricosuric therapy to have an adequate fluid intake, as crystalluria may cause irritation, haemorrhage, and even renal damage. This is especially liable to occur with powerful uricosuric drugs where the margin of safety between therapeutic and excessive dosage may be small. Special caution is necessary when the patient is known to have renal calculi.

None of the patients in this series suffered any genito-urinary side-effects when receiving Urelim, and renal function, estimated by serial determinations of creatinine clearance, remained unaltered during treatment.

There is the risk, common to all uricosuric drugs, of provoking an exacerbation of gout during the early stages of treatment, and uricosuric drugs are not prescribed for treatment of the acute gouty attack. One patient in this series (Case 5) suffered an acute attack of gout after taking Urelim for 10 days, and Case 1 also had an acute attack of gout, but this may have been precipitated by the preceding asthma rather than by the Urelim or probenecid he had taken. It is thought advisable that patients
starting Urelim therapy should receive a maintenance dosage of colchicine during the first 6 weeks of treatment.

Summary

The effect of a new uricosuric agent, p-carboxybenzenesulphadiethylamide (Urelim), has been studied in six patients suffering from gout. It was found to be effective and well tolerated in doses ranging from 500 mg. to 2 g. daily. The only side-effect noted was drowsiness in one patient when a single dose of 1 g. was taken. Two patients who had side-effects with probenecid were able to take Urelim in effective dosage without trouble. Urelim would appear to be useful in the interval treatment of gout. As with other uricosuric drugs, Urelim may provoke acute gouty attacks in the early stages of treatment, and colchicine should be given during the first 6 weeks of treatment.

Comparison has been made between Urelim and other uricosuric drugs, and the effects of Urelim taken in combination with these drugs are also being studied.

We wish to thank Dr. J. M. Simister of Messrs' Ward, Blenkinsop & Co., for supplies of Urelim used in these studies. We also gratefully acknowledge the technical assistance of Mr. J. Watson and Miss P. Ord.

REFERENCES


SUMARIO

En seis enfermos con gota se estudió el efecto de un agente uricosúrico nuevo, p-carboxibenzenosulfadietilamida (Urelim). Se mostró eficaz y bien tolerado en dosis diaria de 500 mg. a 2 g. El único efecto secundario fue somnolencia observada en un enfermo que tomó un gramo a la vez. Dos enfermos que acusaron efectos secundarios con probenecid, tomaron dosis eficaces de Urelim sin dificultad. Urelim parece ser útil en el tratamiento de intervalo de la gota. Como los demás agentes uricosúricos, el Urelim puede provocar ataques agudos de gota al principio del tratamiento y se debe administrar colchicina durante las seis primeras semanas de tratamiento. Se compara el Urelim a otros productos uricosúricos y se estudian los efectos del Urelim asociado a ellos.
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