Studies in laboratory animals to assess the safety of anti-inflammatory agents in acute porphyria

KENNETH E L McCOLL, GEORGE G THOMPSON, AND MICHAEL R MOORE

From the University Department of Medicine, Western Infirmary, Glasgow

SUMMARY The safety of various anti-inflammatory drugs in acute porphyria was assessed by examining their effect on rat hepatic haem synthesis. Azapropazone, chloroquine, and gold increased δ-aminolaevulinic acid (ALA) synthase activity, indicating that they are liable to precipitate porphyric crises. Aspirin, ibuprofen, indomethacin, ketoprofen, flurbiprofen, phenylbutazone, naproxen, prednisolone, and penicillamine did not increase ALA synthase activity and should be safe in porphyria. Though these animal studies can be used as a guide to prescribing in patients with acute porphyria, some caution is still required as species may vary in their response to inducing agents.

Key words: chloroquine, azapropazone, gold, δ-aminolaevulinic acid synthase.

The acute hepatic porphyrias which comprise acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria are examples of pharmacogenetic disease. They are the result of deficiencies of individual enzymes in the pathway of haem biosynthesis and are inherited in an autosomal dominant fashion. Subjects with the genetic trait generally enjoy good health but are at risk of developing severe and life threatening attacks of porphyria if exposed to certain commonly prescribed drugs. Prevention of such attacks depends upon identifying subjects with the genetic trait and preventing them from being exposed to porphyrinogenic drugs. As a result of family screening programmes there has been a marked increase in the number of subjects known to have porphyria and a significant proportion of them will require treatment with anti-inflammatory agents at some time in their life. To provide some guidance concerning their safety in patients with porphyria we have tested 12 commonly prescribed anti-inflammatory agents in laboratory animals.

Materials and methods

The porphyrinogenicity of the drugs was tested by examining their effects on the activity of the rate controlling enzyme of haem biosynthesis δ-aminolaevulinic acid (ALA) synthase in rat hepatic tissue. To confirm the reliability of the animal model, phenobarbitone was also tested. For each drug examined six male Sprague-Dawley rats received the test drug and six control rats received the appropriate placebo solution. The drugs were administered intraperitoneally for three days in a dosage equivalent to 2.5 times the normal human dosage expressed as mg/kg body weight/day. The animals were killed three hours after the final injection, their livers excised, and the activity of hepatic ALA synthase determined as previously described. Statistical comparisons of the test and control animals were performed using the non-parametric Mann-Whitney U test.

Results

The effects of the various drugs on hepatic ALA synthase activity are shown in Table 1. Phenobarbitone resulted in a 214% increase in enzyme activity (p<0.001). Of the eight first line non-steroidal anti-inflammatory drugs studied, only azapropazone significantly affected ALA synthase activity, increasing it by 55% (p<0.05). Of the four second line agents studied, gold increased ALA synthase activity by 56% (p<0.05) and chloroquine increased it by 71% (p<0.05). ALA synthase activity was not affected by prednisolone or penicillamine.
Anti-inflammatory agents in porphyria

be checked by assessing its effect on this enzyme. Ideally, drugs should be tested by assessing their effect on hepatic ALA synthase activity in humans, but this would involve repeated liver biopsies and is again unethical. Consequently, the porphyrino-genicity of drugs is tested by assessing their effect on hepatic ALA synthase in laboratory animals. This method is not totally reliable as there may be slight differences between species in their response to drugs, but currently it is the best available method. In our own clinical practice with patients with porphyria we have found the animal studies a valuable means of guiding our clinical prescribing.

In the animal studies the drug is administered in a dose which is slightly higher than the human dose as false negative results are potentially more damaging to the patients. The drugs are administered to animals by intraperitoneal injection as we have found this to be the only reliable way of being certain that the full dose has been received. Hepatic ALA synthase activity is measured three days after the initial dose as this is the time at which any increase in the enzyme activity will be most marked.

The inclusion of a porphyrinogenic drug, such as phenobarbitone, in the animal studies provides confirmation of the validity of the model and also permits some measurement of the porphyrino-genicity of the drugs being tested relative to the standard.

The finding that azapropazone, chloroquine, and gold increase hepatic ALA synthase activity indicates that these drugs are liable to result in exacerbations of acute porphyria. The degree of increase in enzyme activity with these drugs was less than with phenobarbitone, indicating that they are less potent porphyrinogenic agents. The other drugs tested did not affect ALA synthase and should be safe to use in patients with porphyria. Some caution is required, however, when applying results of animal studies to humans as different species may vary in their response to inducing agents.

There is currently considerable concern about the many adverse effects of anti-inflammatory agents. The elucidation of the biochemical basis of drug induced attacks of porphyria has meant that this particular adverse effect can be predicted and prevented. Hopefully this will also soon be true of some of the other adverse effects of these agents.

References

Discussion

Unfortunately, there is no totally reliable way of determining which drugs are safe and unsafe in patients with acute porphyria. Testing drugs by administering them to patients with porphyria is clearly unethical, and human data therefore depend on anecdotal reports of the effect of treatment of intercurrent diseases in patients with the genetic trait. Such anecdotal reports are difficult to interpret as several drugs have often been prescribed simultaneously, and the intercurrent disease, rather than the drugs, may have triggered the porphyria attack. In addition, only a proportion of patients with porphyria will develop attacks on exposure to porphyrinogenic drugs and anecdotal reports of safety may be misleading. Owing to the rarity of the acute porphyrias and the vast number of prescribable drugs, anecdotal reports only provide very limited information about the safety of drugs in this disease.

The elucidation of the underlying biochemical defect in the acute porphyrias has shown new ways of predicting the effect of drugs on the disorder. Patients with acute porphyria have partial deficiencies of individual enzymes in the pathway of haem biosynthesis. As a consequence there is a compensatory increase in the activity of the initial and rate controlling enzyme of the pathway ALA synthase, resulting in varying degrees of overproductions of porphyrins and porphyrin precursors formed before the enzyme block. Drugs which can precipitate porphyric crises in these patients do so by further increasing ALA synthase activity, and therefore the safety or otherwise of a drug in acute porphyria can

Table 1 Effect of anti-inflammatory agents and phenobarbitone on hepatic ALA synthase activity in rats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg/24 h)</th>
<th>Hepatic ALA synthase activity (as percentage change from control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>10</td>
<td>+214 (p&lt;0.01)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>80</td>
<td>+31</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>50</td>
<td>+55 (p&lt;0.05)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>15</td>
<td>-23</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>40</td>
<td>+4</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>10</td>
<td>-3</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>10</td>
<td>+10</td>
</tr>
<tr>
<td>Naproxen</td>
<td>30</td>
<td>-6</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>20</td>
<td>-14</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>25</td>
<td>+71 (p&lt;0.05)</td>
</tr>
<tr>
<td>Gold (sodium d- aurothiomalate)</td>
<td>0-5</td>
<td>+56 (p&lt;0.05)</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>20</td>
<td>+8</td>
</tr>
</tbody>
</table>


Studies in laboratory animals to assess the safety of anti-inflammatory agents in acute porphyria.
K E McColl, G G Thompson and M R Moore

Ann Rheum Dis 1987 46: 540-542
doi: 10.1136/ard.46.7.540

Updated information and services can be found at:
http://ard.bmj.com/content/46/7/540

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/