INFLUENCE OF LIVER METABOLISM ON THE ACTIONS OF ALTHESIN AND THIOPENTONE

G. P. NOVELLI, M. MARSILI AND P. LORENZI

SUMMARY

To examine the role of liver metabolism on the actions of Althesin, its duration of action and circulatory effects were measured under the following experimental conditions in the rat: (a) non pretreated rats; (b) non pretreated rats: injection through the portal vein; (c) rats with cholestasis; (d) rats with induced microsomal enzymes; (e) rats with a depressed microsomal enzymatic synthesis. The experiments were repeated in the same animals by injecting equivalent doses of thiopentone. The effects of Althesin depend upon the functional conditions of the liver, while a relationship of this kind does not occur with thiopentone.

It has been demonstrated that the brief action of Althesin is the result of a rapid breakdown of the drug by the liver. Card, McCulloch and Pratt (1972) showed that Althesin is concentrated rapidly in the liver and is excreted in the bile. Child and his co-workers (1972) indicated that the sleep time after a single dose of Althesin in rats, with a hereditary deficiency of glucuronyl-transferase, is longer than in normal rats of other strains. However, these experiments were performed on two different strains of rats.

In an attempt to confirm the influence of liver function on the effects of Althesin, the drug was injected into rats of a single strain whose hepatic metabolic activity was normal, increased or decreased; sleep time and cardiovascular disturbance were considered as indices of the effects of the drug. The experiments were repeated in the same animals using equivalent doses of thiopentone.

MATERIALS AND METHODS

Male Wistar rats, 250 g weight, maintained in identical conditions and fed with a standard commercial diet were used in all experiments after a 12-hr fasting period.

During light ether anaesthesia, the right femoral artery and the left femoral vein were cannulated with thin plastic catheters which were advanced to the aorta and vena cava. The arterial catheter was connected to a Statham electromanometer for the continuous measurement of arterial pressure. The venous catheter was used for injecting the test drugs.

In all experiments a mid-line laparotomy was performed and a plastic catheter, which was used for injecting the drugs in the second experimental group only, was introduced into the portal vein through a branch of the superior mesenteric vein. The abdomen was closed. Needle electrodes were used for monitoring the e.c.g.

After complete recovery from the ether anaesthesia the effects of Althesin and of thiopentone were evaluated according to the following criteria:

(a) sleep time: considered as the time between injection of the drug and the reappearance of the spontaneous righting reflex;
(b) decrease of mean arterial pressure; the percentage change from basal values was calculated at 30 sec, 120 sec, and 180 sec after the injections;
(c) decrease of cardiac rate measured from the e.c.g. The rate was calculated also as a percentage of baseline value at 30 sec, 120 sec and 180 sec after injection.

Althesin 0.25 ml/kg and thiopentone 20 mg/kg were injected into each rat according to a randomized sequence; the second drug was injected after complete recovery from the first.

The experiments were performed under the following conditions:

First group (control group). The test drugs were injected through the femoral vein in 10 rats, prepared
as before but not pretreated; five further rats were sacrificed for the determination of glucuronyltransferase enzyme activity.

Second group (portal injection in normal rats). The drugs were injected into the portal vein in 10 rats which were not pretreated. The aim of this experiment was to expose the injected drug to the liver, immediately and in high concentration.

Third group (enzyme induction by pretreatment). Fifteen rats were injected with phenobarbitone 100 mg/kg/day for 7 days given into the peritoneum. The test drugs were injected through the femoral catheter in 10 rats; an additional five rats were sacrificed for enzyme activity measurements.

Fourth group: cholestatic liver damage was induced 8 days before injection of the test drugs by surgical ligation and section of the biliary ducts. Mortality was very high in the period following surgery. The test drugs were injected in 10 surviving rats, through the femoral catheter, while five other rats were sacrificed for enzyme activity determinations.

Fifth group. Inhibition of microsomal synthesis was provoked in 15 rats by pretreatment with d-1-ethionine 100 mg/kg given i.p. every day. The test drugs were injected in 10 surviving rats, through the femoral catheter, while five other rats were sacrificed for enzyme activity estimations.

Hepatic metabolizing activity was tested by measurement of glucuronyl-transferase activity, measured at pH 7.40, according to Van Roy and Heirwegh (1968) and Black, Billing and Heirwegh (1970), the results being expressed as the quantity of bilirubin metabolized per gram of liver per hour.

The SEM was calculated for each group of results and their statistical significance was evaluated using Student's t test comparing each experimental group with the control group.

RESULTS

The effect of the pretreatments on the glucuronyltransferase activity is shown in table I; enzyme activity in rats receiving injections to the portal vein (group 2) was not measured because it was assumed that such values would be identical to those obtained in the control group.

Table II shows that the sleep time after Althesin, but not thiopentone, is related to the degree of hepatic breakdown of the drugs.

Figure 1 shows the changes in mean arterial pressure after Althesin. In groups 2 and 3 (portal-injected and enzyme induced rats) there was significantly less effect on arterial pressure compared with the control group.

Depressor effects of thiopentone on arterial pressure (fig. 2) were less than in the control group only at 30 sec after injection in groups 2 and 3.

Figures 3 and 4 show the effects of Althesin and thiopentone on cardiac rate. The results were very similar to those reported for arterial pressure.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Enzyme activity</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>No pretreatment (controls)</td>
<td>1.243 ±0.031</td>
<td></td>
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<tr>
<td>Phenobarbitone pretreatment</td>
<td>3.543 ±0.000</td>
<td>P&lt;0.01</td>
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<tr>
<td>Surgical cholestasis</td>
<td>0.592 ±0.100</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Ethionine pretreatment</td>
<td>0.444 ±0.083</td>
<td>P&lt;0.01</td>
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</tbody>
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<thead>
<tr>
<th>Groups</th>
<th>Sleep time (min) after injection of Althesin 0.25 ml/kg and of thiopentone 20 mg/kg. 10 rats in each group.</th>
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</thead>
<tbody>
<tr>
<td>Althesin</td>
<td>Thiopentone</td>
</tr>
<tr>
<td>Groups</td>
<td>[min, sec, SEM, P]</td>
</tr>
<tr>
<td>1 No pretreatment, femoral injection</td>
<td>23, 20, 4.28, —</td>
</tr>
<tr>
<td>2 No pretreatment, portal injection</td>
<td>13, 00, 2.42, P&lt;0.05</td>
</tr>
<tr>
<td>3 Phenobarbitone pretreatment, femoral injection</td>
<td>6, 40, 0.61, P&lt;0.01</td>
</tr>
<tr>
<td>4 Surgical cholestasis, femoral injection</td>
<td>44, 55, 3.75, P&lt;0.05</td>
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<tr>
<td>5 Ethionine pretreatment, femoral injection</td>
<td>30, 06, 1.49, P&lt;0.05</td>
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DISCUSSION

These experiments show that variations in liver metabolism may modify the action of Althesin, and confirm that the action of this steroid anaesthetic is limited by rapid breakdown in the liver.

![Graph 1](https://academic.oup.com/bja/article-abstract/47/9/913/263038)

**FIG. 1.** Arterial mean pressure following injection of Althesin 0.25 ml/kg in 0.2 ml.

![Graph 2](https://academic.oup.com/bja/article-abstract/47/9/913/263038)

**FIG. 2.** Arterial mean pressure following injection of thiopentone 20 mg/kg in 0.2 ml.

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Previous investigations (Card, McCulloch and Pratt, 1972; Child et al., 1971, 1972; Child, Gibson and Harnbyg Hart, 1972) proved the role of the liver and the importance of glucuronyl-transferase, although these experiments were performed on rats of different strains.
In our experiments, a single strain of rats was used, and the glucuronyl-transferase activity was increased or decreased by pretreatment. Portal injection showed the effect of passing the drug through the liver before it could enter the general circulation.

The data on thiopentone confirm the view that its action is limited as a result of redistribution and not by metabolic breakdown (Brodie et al., 1950). The drug is present in the organism for a considerable time and this is the basis for the period of "hangover" that follows emergence from barbiturate anaesthesia. Portal injection or pretreatments do not modify the effects of thiopentone on sleep time, on arterial pressure or on cardiac rate.

Our data on Althesin indicate that rapid breakdown occurs in the liver by microsomal enzymes and especially by glucuronyl-transferase. The sleep time and cardiovascular effects of Althesin are greatly reduced by exposing the drug to an increased enzyme activity. The portal injection experiment showed that Althesin breakdown occurs very rapidly in the liver. This is supported by the results obtained in association with cholestasis or a decrease of microsomal enzyme activity.

The depression of liver activity does not modify the cardiovascular effects of Althesin, because although the decrease of hepatic breakdown increases the duration of the effects of the drug, it cannot increase their intensity compared with the control situation. When enzyme activity is increased the cardiovascular effects are reduced because the total dose of the drug acting on the circulation is reduced.

These results are of clinical significance, because it is possible that the duration of Althesin anaesthesia may be increased or decreased according to the functional status of the liver and the degree of its enzyme induction activity.

REFERENCES