THE POSITIVE ROLE OF THE LIVER IN THE RAPID METABOLISM OF THIOPENTAL

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A well supported explanation for the short duration of action of the thiobarbiturates is that the drug is not rapidly destroyed but is rapidly sequestered in fat (1). In apparent conflict with this fact is the demonstration (2, 3) that a decrease in the amount of functioning liver tissue greatly prolongs the effect of thiopental and its disappearance from the plasma of the dog. The conclusion that the liver is important is in conflict with much of the earlier animal work (4, 5) and especially with the comprehensive report of Masson and Beland (6) in which they concluded that thiopental is detoxified in all tissues except the liver and kidneys. In view of this conflict in experimental results, the present study was undertaken.

In previous work, the duration of effect of a standard dose of thiopental in a control animal, that is, untreated or unoperated, was compared with the effect on an animal in which carbon tetrachloride or a surgical procedure under anesthesia had been used to destroy the liver partially. Such a comparison does not allow for the effect of previous anesthesia or for the deteriorative changes other than the specific loss of liver function.

The improvements in technique in this study are two. First, the test dose of thiopental was not given a day or more after the damaging procedure, but the surgical anesthetic dose was also the dose for which the duration of action was determined. Second, in order to achieve complete rather than partial destruction of liver function and in order to perform hepatectomy within the time allowed by a single dose of thiopental, the liver was not removed, but a "functional hepatectomy" was performed by ligating the blood supply to the liver after establishing an Eck fistula.

METHODS

Dogs weighing between 7 and 11 kg. were selected in order to reduce the variability in response noted in preliminary experiments when,

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after a constant dose per kilogram of thioptental, smaller animals recovered more rapidly and larger animals slept longer.

In order to exclude the liver rapidly from the circulation, portal flow was diverted through an Eck fistula and the portal vein and hepatic artery were then ligated. Thioptental sodium, 20 mgm. per kilogram, was given intravenously after all preparations for operation were completed. An Eck fistula was prepared following the procedure of Markowitz (7) except that a midline incision was used in order to shorten this procedure. A heavy tie was placed about the portal vein and hepatic artery high in the fissure and without freeing the structures from the gastrohepatic ligament. For controls, sham operations on animals were performed, that is, the portal vein and vena cava were joined but no stoma was cut and a ligature was placed through the edge of the gastrohepatic ligament but not tied.

<table>
<thead>
<tr>
<th>Minutes from Injection of Thioptental until Animal</th>
<th>Swallowed</th>
<th>Stretched</th>
<th>Raised Head</th>
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<tbody>
<tr>
<td>Sham heptectomy</td>
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<td>51</td>
<td>49</td>
<td>71</td>
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<td>83</td>
<td>66</td>
<td>89</td>
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<tr>
<td>Laparotomy only</td>
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<td>28</td>
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<td>38</td>
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<tr>
<td>Ave. 36</td>
<td>Ave. 24</td>
<td>Ave. 66</td>
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</table>

The duration of effect was determined by recording the times after injection at which the dog first swallowed, stretched his limbs and raised his head completely off the floor, all without stimulation.

RESULTS AND DISCUSSION

Comparison of the times for recovery of the heptectomized and sham operated dogs showed a great prolongation of effect resulting from exclusion of the liver. There was an interval of twenty-six to thirty minutes from the time of injection of the anesthetic until the ligature about the portal vein and hepatic artery was tied and closure was begun. At the conclusion of the procedure, the animals of both groups were regaining muscle tone and responding by increased respiratory rate to the painful stimulation. Sham operated animals then recovered after only a slight delay (table 1). In the experimental group, except for relaxation at the end of the operation, no change in the depth of anesthesia was seen. Four animals in which the pro-
cEDURE was completely satisfactory and there were no signs of recovery were sacrificed one and a half, three and a half, four and a half and six hours after the injection of the anesthetic agent. Two additional animals were killed by procedures unrelated to this experiment two hours after the anesthetic was administered and 2 more are not discussed because of cyanosis of the abdominal contents and a small stoma in the Eck fistula at autopsy.

That the change in duration of thiopental effect was due specifically to the elimination of functioning liver tissue and not to the surgical procedure in general was shown by comparison with the sham operated animals. That the operated animals could have recovered had the thiopental been eliminated was shown by two types of experiments. First, one animal was operated on under ether anesthesia and recovered promptly from the volatile anesthetic. Second, 2 animals were given an analeptic (amphetamine in one case, pentylentetrazol in the other) at the end of the experiment three and a half and four and a half hours after the injection of the anesthetic, and were able to respond by lightening of the anesthesia to a stage of marked excitement.

Dogs whose liver was by-passed as described remained in good condition. Blood pressure was unaffected except for a fall during the actual surgical procedure. The abdominal viscera were also cyanotic only transiently. Hypoglycemia appeared as rapidly as in heptectomized dogs. In 2 animals shock relieved by intravenous administration of glucose appeared one and a half and two hours after the ligation. Other animals were given glucose periodically, beginning one hour after the operation.

Also included in table 1 are the times for recovery of animals subjected to laparotomy only. These data demonstrate the prolongation caused by interference during the operation with portal blood flow and also permit an evaluation of the criteria of awakening which were used.

These results support the conclusion that the liver is important in the metabolism of thiopental. This fact is not surprising in view of recent in vitro studies (8), and the criticisms to which earlier in vivo work have been subjected (2). In addition, since the technique used in this work is equivalent to total removal of the liver and, since recovery did not occur within several hours, the impression that all other tissues are quantitatively unimportant in the rapid recovery from thiopental seems justified. These animals received only anesthetic doses of thiopental, and it is difficult to understand why the fat depots should not have been able to extract the agent if unmodified thiopental is the substance found in fat.

Summary

Liver function in dogs was eliminated by ligation of the portal vein and hepatic artery after an Eck fistula was established. When this procedure was carried out under thiopental anesthesia, the animals did
not show signs of awakening during a period of at least four times that necessary for sham operated animals to recover. It is believed that tissues other than the liver are quantitatively unimportant in the rapid detoxification of thiopental in the dog.

REFERENCES


INTERNATIONAL CONGRESS ON GYNECOLOGY AND OBSTETRICS

The International Congress of Gynecology and Obstetrics will be held in Geneva from July 26 to July 31, 1954. An Information Bulletin describing the organization of the Congress has been prepared and can be obtained from the Secretariate of the Congress, Maternite, Geneva, Switzerland, or in all branches of the American Express Company.