EFFECTS OF CORTISONE ACETATE ON BARBITAL ANESTHESIA IN NORMAL RABBITS

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In the previous reports (Komiya and Shibata, 1956 a, b) it was demonstrated that the abnormal onset and duration of barbital anesthesia induced by adrenalectomy in mice were nearly restored to the normal by cortisone treatment and that barbital concentration in the brain was increased by adrenalectomy but was decreased by cortisone not only in adrenalectomized but also in normal mice.

The present experiment is concerned with the temporary effect of cortisone acetate on barbital anesthesia, on barbital concentration in the blood, on barbital amount in the urine and on body temperature in normal rabbits.

MATERIALS AND METHODS

Four male adult rabbits weighing approximately 2 kg were employed in the present experiment.

Control experiment: As the control experiment three of the animals received subcutaneously 2 cc of saline solution once a day for 2 successive days and then they were injected intravenously with 170 mg per kg of barbital-Na (sodium diethylbarbiturate, Daiichi Kagaku Co.; abbreviated here as barbital) at 24 hours after the last injection of the saline. The depth of anesthesia was determined by the Sakamoto’s (1935) six grades (0 to VI), every 5 minutes within 30 minutes and thereafter every 30 minutes until 8 hours after the injection.

The barbital concentration in the blood withdrawn from ear vein was measured by Butler’s method (1950), using a Beckman spectrophotometer at 5 and 30 minutes, 1, 2, 4, 6 and 8 hours after the injection. Barbital concentration in the urine obtained by means of urether catheter was measured similarly at 45 minutes, 3 and 5 hours after the injection.

Body temperature was measured by rectal thermometer for animal use.

Cortisone acetate experiment: One week after the control experiment the animals were injected subcutaneously with 25 mg of cortisone acetate (Cortone Acetate, Merck & Co.; abbreviated here as CA) in 2 cc of saline once a day for 2 successive days. Then, similarly as in the control experiment, they were injected intravenously with barbital and the depth of anesthesia, the barbital concentration in the blood and urine and body temperature were measured.

Repeated injection experiment: One of the 4 animals received saline solution instead of CA to observe the influence of repeated injection.

Received for publication January 30, 1957.
RESULTS

Figures 1, 2 and 3 illustrate graphically the results of the control and CA experiments and Figure 4 those of repeated injection.

1. The depth of barbital anesthesia
As seen in Figures 1, 2 and 3, the depth of anesthesia in the control experiment increased rapidly after barbital injection attaining grade V within 30 minutes in 2 animals and within an hour in one. Time interval to attain grade VI was an hour in one case and 1.5 hours in the other 2. Thereafter the depth of anesthesia decreased gradually and waking-time was 7.5 hours in 2 cases and 8 hours in one.

In CA experiment all animals attained grade V within 30 minutes after barbital injection and grade VI within 1.5 hours. Thus the induction time of barbital anesthesia for CA experiment was not significantly different from that for control. While the depth of anesthesia after 4 hours following barbital injection for CA experiment decreased earlier than that for control; waking-time was 6.5 hours in one case and 7 hours in 2. Thus the waking-time tended to be shortened by CA treatment.

As seen in Figure 4, the depth of barbital anesthesia in the second time in repeated injection experiment was almost in accord with that in the first.

2. Barbital concentration in the blood
At an hour after the barbital injection the concentration in the blood of both control and CA experiments decreased abruptly and thereafter gradually. No significant difference was observed between both of them.

As seen in Figure 4, barbital concentration in the blood in the second time in repeated injection experiment was almost in accord with that in the first.

On the basis of these results, it may be considered that CA does not affect the barbital concentration in the blood.

3. Barbital amount in the urine
As shown in Table 3 and Figures 1, 2 and 3, barbital amount in the urine at 45 minutes, 3 and 5 hours after the injection in CA experiment increased significantly in comparison to that in control. As seen in Table 2, urine amount in CA experiment increased in 2 cases and did not change in one in comparison to that in control. Changes in barbital amount in the urine were not always parallel to those in urine amount.

In repeated injection experiment shown in Figure 4 and in Table 4, urine amount at 45 minutes and 3 hours after the injection in the first time exceeded that in the second time and at 5 hours the result was reversed. But the total amount of barbital excreted in the urine during 5 hours after the injection was almost same in both cases.

4. Body temperature
Body temperature in both control and CA experiments decreased by and by with the progress of anesthesia and increased to normal level towards awakening. These changes in body temperature were not different from those in repeated injection experiment.
Fig. 1. Effect of cortisone acetate on barbital anesthesia Rabbit No. 1
- Depth of anesthesia, ○ Barbital concentration in blood, △ Body temperature
- Control experiment, — CA experiment
- Barbital amount in urine in control experiment
- Barbital amount in urine in CA experiment
Remarks same for Figures 2 and 3

Fig. 2. Effect of cortisone acetate on barbital anesthesia Rabbit No. 2
Fig. 3. Effect of cortisone acetate on barbital anesthesia
Rabbit No. 3

Fig. 4. Effect of repeated saline injection on barbital anesthesia
Rabbit No. 4
- Depth of anesthesia,  • Barbital concentration in blood, △ Body temperature
  For the first time, — For the second time
□ Barbital amount in urine for the first time
■ Barbital amount in urine for the second time
DISCUSSION

Winter and Flataker (1951, 1952) found that cortisone markedly reduced the effect of morphine or methadon upon the reaction time of the tail-flick response to thermal stimuli in normal rats and that it prolonged the induction time and shortened the sleeping time of ether anesthesia in mice. From these results they attributed the effects to central stimulating action of the steroid. The demonstration that cortisone reduces the electroshock seizure threshold (EST) in rats (Woodbury and Sayers, 1950; Woodbury et al., 1951; Woodbury, 1952) is also in accord with this view. On the other hand Komiya and Shibata (1956a, b) reported that the shortening of the duration of barbital anesthesia by cortisone

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**Table 1. Effect of cortisone acetate on barbital concentration in blood (µg/cc)**

<table>
<thead>
<tr>
<th>Time after barbital inj. (min.)</th>
<th>Rabbit number and injection</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>CA</td>
<td>Saline</td>
<td>CA</td>
<td>Saline</td>
</tr>
<tr>
<td>5</td>
<td>223.29</td>
<td>275.35</td>
<td>227.21</td>
<td>255.45</td>
<td>267.93</td>
</tr>
<tr>
<td>30</td>
<td>213.16</td>
<td>256.69</td>
<td>213.60</td>
<td>251.33</td>
<td>235.45</td>
</tr>
<tr>
<td>60</td>
<td>205.35</td>
<td>213.60</td>
<td>201.23</td>
<td>224.54</td>
<td>213.70</td>
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<tr>
<td>120</td>
<td>186.18</td>
<td>204.73</td>
<td>199.99</td>
<td>212.15</td>
<td>202.67</td>
</tr>
<tr>
<td>240</td>
<td>175.25</td>
<td>175.25</td>
<td>184.11</td>
<td>188.86</td>
<td>166.38</td>
</tr>
<tr>
<td>360</td>
<td>169.68</td>
<td>156.69</td>
<td>173.19</td>
<td>169.68</td>
<td>152.73</td>
</tr>
<tr>
<td>480</td>
<td>154.17</td>
<td>153.39</td>
<td>170.26</td>
<td>146.57</td>
<td>138.34</td>
</tr>
</tbody>
</table>

**Table 2. Effect of cortisone acetate on urine amount (cc)**

<table>
<thead>
<tr>
<th>Time after barbital inj. (min.)</th>
<th>Rabbit number and injection</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Saline</td>
<td>CA</td>
<td>Saline</td>
<td>CA</td>
<td>Saline</td>
</tr>
<tr>
<td>0-45</td>
<td>2.9</td>
<td>16.4</td>
<td>2.9</td>
<td>12.0</td>
<td>21.1</td>
</tr>
<tr>
<td>46-180</td>
<td>3.8</td>
<td>4.0</td>
<td>3.8</td>
<td>6.8</td>
<td>36.5</td>
</tr>
<tr>
<td>181-300</td>
<td>4.0</td>
<td>11.5</td>
<td>4.0</td>
<td>3.9</td>
<td>46.0</td>
</tr>
<tr>
<td>Total</td>
<td>10.7</td>
<td>31.9</td>
<td>10.7</td>
<td>22.7</td>
<td>103.6</td>
</tr>
</tbody>
</table>

**Table 3. Effect of cortisone acetate on barbital amount in urine (µg/cc×urine amount)**

<table>
<thead>
<tr>
<th>Time after barbital inj. (min.)</th>
<th>Rabbit number and injection</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
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<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>CA</td>
<td>Saline</td>
<td>CA</td>
<td>Saline</td>
</tr>
<tr>
<td>0-45</td>
<td>397.16</td>
<td>1409.58</td>
<td>514.43</td>
<td>1051.92</td>
<td>1892.41</td>
</tr>
<tr>
<td>40-180</td>
<td>1444.57</td>
<td>3835.60</td>
<td>1099.47</td>
<td>3006.71</td>
<td>2746.88</td>
</tr>
<tr>
<td>181-300</td>
<td>515.00</td>
<td>2158.09</td>
<td>1000.40</td>
<td>1549.39</td>
<td>2245.61</td>
</tr>
<tr>
<td>Total</td>
<td>2356.73</td>
<td>7703.27</td>
<td>2614.30</td>
<td>5608.02</td>
<td>6884.90</td>
</tr>
</tbody>
</table>
in adrenalectomized or normal mice was considered to be due to the decrease of barbital concentration in the brain induced by the steroid. But it is not clear what is the predominant factor governing the discharge of barbital from the brain. Koppanyi and Linegar (1942) reported that the drug was released from the brain when its concentration in the blood fell and its binding with the nerve tissue was loose. Also Goldbaum and Smith (1954) reported that the binding of barbital to bovine serum albumin and rabbit tissue homogenate was looser than that of other barbiturates.

In the present experiment, no significant difference was observed in barbital concentration in the blood between CA and control experiments, while barbital amount in the urine in the former exceeded that of the latter and anesthesia time was shortened in the former, indicating some relations between the two phenomena.

As the functional factors determining the barbital concentration in the blood, the destruction or chemical alteration principally in the liver, and distribution or excretion through the kidney are considered. And the fate of a particular barbiturate must depend upon its chemical constitution, though at present one cannot predict from the chemical structure precisely how the drug will be mobilized. According to Maynert and VanDyke (1949), barbital, one of the long-acting barbiturates, is relatively stable, and indeed it appears in the urine in measurable quantities. Renzi et al. (1956) studied the effect of cortisone in adrenalectomized rats on the experimental syndrome of water intoxication and on creatinine and paraaminohippurate clearance, and they reported that the steroid stimulated water diuresis both in the water intoxication and in the renal clearance experiments.

On the basis of such viewpoints, it may be inferred that the increase in barbital amount in the urine induced by cortisone treatment in the present experiment is due to the acceleration of water excretion, renal clearance of barbital and its release from the brain and other organs. That no significant difference was observed in barbital concentration in the blood between the treated and control experiments is considered due to the fact that the increase of barbital amount released from various organs by cortisone treatment is parallel to that excreted in the urine.

Concerning body temperature no significant change was observed in this study: it decreased gradually with the progress of anesthesia and with awakening returned to normal in either control or in CA experiment.

SUMMARY

Using male rabbits the effects of cortisone acetate upon the barbital anesthesia were investigated with the following results:

1. The depth of anesthesia attained the maximum at 1.5 hours after the injection in both control and CA experiments.
2. Waking-time tended to be shortened by CA treatment.
5. Body temperature did not change significantly by CA treatment.
ACKNOWLEDGMENTS

The authors are indebted to Dr. Charles A. Winter, Merck Institute, West Point, Pennsylvania, for the cortisone acetate used here. Mr. S. Miyashita, Endocrinological Laboratories of Gunma University, kindly helped the measurement of barbital in the blood and in the urine.

REFERENCES