EFFECT OF SYNTHALIN A ON RENAL FUNCTION IN DAIRY BULL CALVES AS MEASURED BY PHENOLSULFONPHTHALEIN CLEARANCE 1

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SUMMARY

Synthalin A (decamethylenediguanidine) is a toxic, hypoglycemic agent which has been reported to cause histological changes in the liver, kidneys, and alpha cells of the Islets of Langerhans, and also to depress hepatic function in dairy bull calves. Five Holstein bull calves (eight days of age) were treated with a single intramuscular injection of synthalin A at the rate of 2.2 mg. per kilogram of body weight. Renal function as measured by both phenolsulfonphthalein fractional and volume clearances was depressed to approximately 35% of normal within 16 hr., and had returned to near-normal values within seven days. Correspondingly, plasma glucose levels decreased from a mean preinjection level of 85.6 mg. % to 32.8 mg. % at 16 hr. after injection, and returned to normal levels again within 66 hr. after injection. These effects were significant statistically (P < 0.01).

Synthalin A (decamethylenediguanidine) was synthesized in 1926 by German investigators (7) who were attempting to produce an orally active substitute for insulin. The material was effective in controlling the hyperglycemia of diabetics, but its use was discontinued because of its severe toxicity.

Several workers (4, 5, 6) have shown that synthalin A caused degenerative changes in the alpha cells of the Islets of Langerhans, the presumed source of a hyperglycemic-glycogenolytic factor, glucagon.

Richards and Weaver (13) and Mixner et al. (12) have shown that synthalin A is a hypoglycemic agent in dairy cattle. Mixner et al. (12), in addition, reported a decrease in liver function as measured by sulphobromophthalein (BSP) fractional clearance.

Blatherwick et al. (3) reported that synthalin A in rabbits caused extensive damage to the cells of the convoluted tubules but not to the glomeruli of the renal nephrons. Davis (4), also working with synthalin A in rabbits, found a severe necrosis of the proximal convoluted tubules of the renal nephrons, along with evidence of liver damage.

The purpose of this investigation was to determine if synthalin A has a detrimental effect on renal function in dairy bull calves as measured by phenolsulfonphthalein clearance (11) and, if so, to implicate the damaged kidney as another causative factor in the hypoglycemic action of synthalin A. A brief report has been made on this study (1).

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METHODS AND PROCEDURES

Five Holstein bull calves were used in this experiment, each animal serving as its own control. Renal function was determined in these animals, using phenolsulfonphthalein (PSP) clearance measures (2, 11).

A single intramuscular injection of synthalin A was given each animal at the rate of 2.2 mg. per kilogram of body weight at 5 P.M. on the eighth postnatal day. The PSP clearance tests were performed on each animal on the seventh, eighth, ninth, and 16th postnatal days between 9 and 10 A.M. Thus, the determinations performed on the seventh and eighth days served as controls, the determination on the ninth day (16 to 17 hr. after synthalin A injection) showed the effects of the synthalin A, and the determination on the 16th day was to show the nature of the recovery.

Blood plasma glucose levels were determined by the glucose oxidase enzyme method (16) on samples collected at 9 A.M. on the seventh, eighth, ninth, tenth, 11th, and 16th days of age.

RESULTS AND DISCUSSION

Mean PSP clearance measures and plasma glucose levels for the five animals are presented in Table 1. An analysis of variance indicated that the PSP fractional clearances and the PSP volume clearances on Day 9 (16 hr. after synthalin A) were significantly lower than the corresponding control values on Days 7 and 8 (P < 0.01). The PSP volumes of distribution (per cent of body weight) were not significantly affected by the treatment. PSP fractional clearances and PSP volume clearances (milliliter of plasma per minute per kilogram of body weight) were reduced to 37.4 and 32.2% of normal, respectively (comparison of ninth-day values to mean of seventh- and eighth-day values). Renal function was approaching normal by the 16th day (seven days after treatment).

Plasma glucose levels fell from a mean of 85.6 mg.% on Days 7 and 8 (prior to synthalin A) to 32.8 mg.% 16 hr. after the administration of synthalin A.

<table>
<thead>
<tr>
<th>Physical condition</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>16 hr. after synthalin A</th>
<th>Recovery phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg.)</td>
<td>44.8</td>
<td>45.1</td>
<td>45.2</td>
<td>......</td>
<td>......</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mg. %)</td>
<td>87.2</td>
<td>83.9</td>
<td>32.8</td>
<td>54.3</td>
<td>100.4</td>
<td>84.6</td>
<td></td>
</tr>
<tr>
<td>PSP fractional clearance (per min.)</td>
<td>0.0237</td>
<td>0.0288</td>
<td>0.0102</td>
<td>......</td>
<td>......</td>
<td>0.0220</td>
<td></td>
</tr>
<tr>
<td>PSP volume of distribution (ml.)</td>
<td>9,600</td>
<td>9,700</td>
<td>9,300</td>
<td>......</td>
<td>......</td>
<td>10,300</td>
<td></td>
</tr>
<tr>
<td>Per cent of body weight</td>
<td>23.1</td>
<td>22.9</td>
<td>20.2</td>
<td>......</td>
<td>......</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>PSP volume clearance ml/min</td>
<td>224</td>
<td>268</td>
<td>82</td>
<td>......</td>
<td>......</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>ml/min/kg body weight</td>
<td>5.27</td>
<td>6.09</td>
<td>1.83</td>
<td>......</td>
<td>......</td>
<td>5.07</td>
<td></td>
</tr>
</tbody>
</table>
a significant decline (P < 0.01). Plasma glucose levels returned to normal or above within 66 hr. after synthalin A treatment.

All calves showed some outward signs of toxicity to the synthalin A. This was characterized by general lethargy, lassitude, and apathy. However, the animals did continue to eat and move about in their pens. Recovery by outward appearances was rapid, paralleling the return of blood glucose levels to normal.

Phenolsulfonphthalein (PSP or phenol red) was shown by Marshall and Vickers (10) and others (8, 9, 14) to be eliminated from the kidneys primarily by proximal tubule secretion. Since synthalin A causes damage to the proximal tubules (4), it is not surprising that the PSP clearance measures were effective in showing depressed functional activity of these tubules. Similarly, the hypoglycemia caused by synthalin A also may be related to the proximal tubule damage, since the site of glucose reabsorption after glomerular filtration is acknowledged to be the proximal convoluted tubules (15). These data tend to validate the measures of renal function as previously described (2, 11).

REFERENCES