DATA EVALUATION RECORD

TRICHLORFON

Acute and Subchronic Toxicity (and antidotal effects) in Calves


REVIEWED BY:

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Date: 6/05/83
STUDY TYPE: Acute and subchronic toxicity (and antidotal effects) in calves.


ACCESSION NUMBER: Not available.

MRID NUMBER: Not available.

LABORATORY: Not available.

TEST MATERIAL: Trichlorfon (purity not specified).

PROTOCOL:

1. Trichlorfon (Neguvon, purity not specified) manufactured by Farbenfabriken, Bayer, AG, was the test compound.

2. The experiment was performed on 16 calves of the Bulgarian brown strain which were 2-4 months old (weight not specified).

3. A 10 percent aqueous solution of trichlorfon was administered orally at dosages of 0.007-0.46 ml/kg [equivalent to 1.21 - 79.58 mg/kg]. The calves received single or multiple treatments (see Table 1). The antidotal effects of the following compounds were studied: 2.5 percent oil-lanolin emulsion with atropine sulfate (OLEAS), paverin-atropium (PA), diethazine hydrochloride (DC), benactizine (B), sodium bicarbonate (NaHCO₃), and tricalcium phosphate (TCP; see Table 2 for doses and routes of administration).

4. The activity of whole blood, plasma, and erythrocyte acetylcholinesterase and the following blood chemistry parameters were determined at various intervals during treatment: total protein, calcium, magnesium, phosphorus, glucose, SGOT, and SGPT.

RESULTS:

Table 1 presents the results obtained in calves treated with different amounts of trichlorfon following single or repeated administration.
<table>
<thead>
<tr>
<th>Animal No. and Dosage</th>
<th>Clinical Observations</th>
<th>Whole Blood Cholinesterase Inhibition&lt;sup&gt;a&lt;/sup&gt; (percent)</th>
<th>Blood Sugar (percent increase)</th>
<th>Recovery/Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1.21 mg/kg</td>
<td>None</td>
<td>15 after 2 hrs&lt;br&gt;30 after 24 hrs</td>
<td>–</td>
<td>Recovery by day 5</td>
</tr>
<tr>
<td>4-3.46 mg/kg (day 1)</td>
<td>Epigastric distention (+30 min)&lt;br&gt;tachycardia, dyspnea, 175 percent tachypnea, loss of appetite, disturbed coordination — instability in hind quarters. (Urine positive for sugar).</td>
<td>60 after 1 hr&lt;br&gt;PChe, 50 after 1 hr&lt;br&gt;EChe, 20 after 1 hr</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>13.84 mg/kg (day 2)</td>
<td>Epigastric distention, mild depression, decrease in appetite, etc. Normal on day 4.</td>
<td>70 after 1 hr&lt;br&gt;80 on day 3&lt;br&gt;22 on day 8&lt;br&gt;Normal on day 10</td>
<td>100&lt;br&gt;Normal on day 3</td>
<td></td>
</tr>
<tr>
<td>5-55.36 mg/kg (day 1)</td>
<td>Anorexia, dyspnea, groaning, ataxia, etc.</td>
<td>70 after 1 hr&lt;br&gt;PChe 90 after 1 hr&lt;br&gt;EChe 80 after 1 hr</td>
<td>15 on day 1&lt;br&gt;100 on day 4&lt;br&gt;PChe, EChe—95 on day 4</td>
<td>90 on day 2&lt;br&gt;Normal on day 3</td>
</tr>
<tr>
<td>6.92 mg/kg (day 4)</td>
<td>Intoxication</td>
<td>--</td>
<td>--</td>
<td>Death in 1 hr</td>
</tr>
<tr>
<td>6-69.2 mg/kg (day 1)</td>
<td>Toxicity signs more severe than animal 5.</td>
<td>PChe, EChe 80-90 on day 1, and&lt;br&gt;100 on day 2 and 3</td>
<td>200 on day 1</td>
<td></td>
</tr>
<tr>
<td>6.92 mg/kg (day 2)</td>
<td>Intoxication</td>
<td>Normal on day 10&lt;br&gt;100 on day 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>PChe: Pseudocholinesterase, EChe: Ethanolcholinesterase
TABLE 1. Summary of Results with Trichlorfon Treated Calves (Cont'd.)

<table>
<thead>
<tr>
<th>Animal No. and Dosage</th>
<th>Clinical Observations</th>
<th>Whole Blood Cholinesterase Inhibition&lt;sup&gt;a&lt;/sup&gt; (percent)</th>
<th>Blood Sugar (percent increase)</th>
<th>Recovery/Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>7, 10, 14-79.58 mg/kg (day 1)</td>
<td>Respiratory distress, asphyxia, tense extremities, muscle weakness, disturbed coordination</td>
<td></td>
<td></td>
<td>Death between 40 min—12 hrs</td>
</tr>
<tr>
<td>3-6.92 mg/kg/day (for 10 days)</td>
<td>Diarrhea, ataxia, bradycardia, bradypnea, decreased appetite, epigastric distention</td>
<td>PChE, EChE 35 after 1-3 hr; 50-80 on day 2; 100 on days 4-10; 75 after 17 days</td>
<td>20 after 1 hr Normal on day 18</td>
<td>Recovery by day 18</td>
</tr>
</tbody>
</table>

<sup>a</sup>PChE, plasma cholinesterase; EChE erythrocyte cholinesterase.
(10 days). Single treatment at 1.21 mg/kg produced no adverse clinical signs, and slight cholinesterase inhibition. The animal recovered by day 6.

Single dosages of 3.46, 55.36, and 69.2 mg/kg followed later by single doses of 13.84, 6.92, and 6.92 mg/kg, respectively, produced clinical signs of toxicity, severely depressed blood, plasma, and erythrocyte cholinesterase, elevated blood sugar, and miscellaneous other indications of systemic toxicity. Death resulted in only one of the 3 cases. Single dosages of 79.58 mg/kg resulted in death to all 3 calves within 40 minutes to 12 hours.

Daily administration of 6.92 mg/kg/day for 10 days resulted in clinical signs of toxicity, decreased cholinesterase levels, and increased blood sugar values, all returning to normal 8 days following the final administration.

Table 2 presents the results obtained in calves treated with 79.58 mg/kg trichlorfon along with various antidotal treatments. Only one of 7 animals died from treatment with this demonstrated lethal dosage.

CONCLUSIONS:

Trichlorfon at a dosage of 1.21 mg/kg produced no permanent toxic effect, while dosages of 3.46, 55.36, and 69.2 mg/kg produced evidence of systemic toxicity (clinical signs, cholinesterase inhibition, and elevated blood sugar) and a dosage of 79.58 mg/kg was lethal. Repeated administration of 6.92 mg/kg (10 days) produced evidence of systemic toxicity, which was reversed by 8 days after the administration of the last dose.

When antidotal treatment with atropine was administered along with a lethal dosage (79.58 mg/kg) of trichlorfon, the animals recovered.

An indication and characterization of the toxic effect produced by trichlorfon was demonstrated by this study. However, in the opinion of this reviewer, a larger number of animals per group and the use of control animals would be required for a more complete understanding of the compound's effect. With respect to cholinesterase and other biochemical parameters, individual data are essential to provide a clear understanding of the results.

CORE CLASSIFICATION: Supplementary data.

The number of animals used per dose level was small, and the purity of the test materials was not specified, limiting the usefulness of these data.
<table>
<thead>
<tr>
<th>Animal No. and Dosage</th>
<th>Clinical Observations</th>
<th>Whole blood Cholinesterase inhibition (percent)</th>
<th>Blood Sugar increase</th>
<th>Recovery/Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-79.58 mg/kg (OLEAS-0.2 ml/kg + NaHCO3-0.5 ml/kg + Ca3P04-0.35 ml/kg)</td>
<td>Gastric distention, disturbed coordination, reduced respiratory rate, salivation, tachycardia</td>
<td>65 after 1 hr; PChE 30 after 1 hr; EChE 80 after 1 hr; 100 after 3 hr.</td>
<td>40 after 3 hr</td>
<td></td>
</tr>
<tr>
<td>18- Same as above</td>
<td>Same as above with mild cyanosis</td>
<td>80 after 3 hr; PChE 100 after 3 hr; EChE 60 after 3 hr.</td>
<td>34 after 1 hr Normal after 15 hr</td>
<td>Death after 15 hr</td>
</tr>
<tr>
<td>9-79.58 mg/kg (OLEAS-0.3 ml/kg + NaHCO3-0.5 ml/kg + Ca3P04-0.35 ml/kg) (benactizene 200 μg/kg, after 3 hr)</td>
<td>Same as above</td>
<td>Same as No. 2</td>
<td>Normal on day 5</td>
<td></td>
</tr>
<tr>
<td>11, 12, 13, 16-79.58 mg/kg (OLEAS-0.3 ml/kg (papaverine-atropine 0.1 ml/kg)</td>
<td>Same as above</td>
<td>30-40 after 1 hr; 80-90 on day 2; Normal on day 14.</td>
<td>Normal on day 6-8</td>
<td></td>
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</tbody>
</table>