EFFECTS OF IMIDOCARB ON CHOLINESTERASE ACTIVITY AND GROSSLY OBSERVABLE BEHAVIOUR IN DOGS

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ABSTRACT

Imidocarb dipropionate, a carbanilide derivative, is used for the treatment of babesiosis and ehrlichiosis in canines. Parenteral administration of imidocarb produced cholinergic symptoms like profuse salivation, restlessness, lacrimation, frequent defecation and panting which may be related to its potential to inhibit acetylcholinesterase activity in blood and plasma. The extent of inhibition of plasma cholinesterase (ChE) and erythrocyte acetylcholinesterase (AChE) activities was higher on intravenous than intramuscular administration. However, duration of inhibition was comparatively prolonged on intramuscular administration of imidocarb dipropionate. The inhibition of cholinesterase activity might have resulted into increased acetylcholine level which resulted into various cholinergic symptoms. Prior treatment of dogs with atropine (0.01 mg/kg, i/v) have been found to block the clinical signs of toxicity when imidocarb was administered by intramuscular route but reduced the severity of clinical signs of imidocarb given intravenously. Therefore, the clinical or toxic cholinergic signs may be due to cholinomimetic effects of imidocarb dipropionate as a result of inhibition of blood cholinesterase and plasma cholinesterase activities which could be blocked or reduced by prior administration of atropine sulphate and help in preventing or lessening various clinical or toxic cholinergic symptoms.

Key words: Imidocarb, cholinesterase, cholinomimetic effects, dogs

Imidocarb dipropionate, a carbanilide derivative, is administered to different species of animals by subcutaneous or intramuscular route for the treatment of protozoal diseases. In dogs, imidocarb is drug of choice for treatment of babesiosis and ehrlichiosis (Blood and Radostitis, 1989) and is less toxic than other antibabesial drugs (Roberson, 1977). Parenteral administration of imidocarb has been found to cause systemic side effects (Abdullah et al., 1984) related to cholinergic stimulation. The present investigation aims on the effects of imidocarb dipropionate on cholinesterase activity in erythrocytes and plasma in dogs following its administration through i/v and i/m routes.

MATERIALS AND METHODS

Five apparently healthy mongrel dogs of either sex were used for this study in three phases at an interval of 4 weeks. In phase I and II, imidocarb was given intravenously and intramuscularly at the rate of 6.5 mg/kg body weight to study the effect of imidocarb on erythrocyte acetylcholinesterase and plasma cholinesterase levels. The animals were provided standard dog feed and water ad libitum. Dogs were acclimatised for one month during which they were protected against rabies by inoculating antirabies vaccine. The drug solution was prepared in such a way that each dog received one ml of drug solution per 10 kg of body weight.

Blood samples for cholinesterase studies were collected in heparinized test tubes before and at 15, 30 min and 1, 2, 4, 6, 9, 12 and 24 h after administration of imidocarb dipropionate by both routes and stored in refrigerator at 0°C until analyzed. An interval of four weeks was allowed between i/v and i/m administration of drug. Erythrocyte acetylcholinesterase (AChE) and plasma cholinesterase (ChE) activity was estimated by modified acetylthiocholine/5,5-dithiobis-2-nitrobenzoic acid (DTNB) procedure by Voss and Sachsse (1970). The blood samples were processed at the earliest after collection and cholinesterase activity was determined in whole blood and plasma (ChE) taking 0.02 ml of...
whole blood. Erythrocyte acetylcholinesterase (AChE) was then determined by subtracting the ChE activity value from that obtained with whole blood. Mean of the AChE and ChE activities of five individual dogs were calculated and expressed as mean ± S.E.

In phase III, the grossly observable behavioural signs of imidocarb dipropionate were observed after i/v or i/m administration at a dose rate of 6.5 mg/kg. To study the effect on behavioural responses of dog to imidocarb dipropionate, atropine sulphate (0.01 mg.kg⁻¹, i/v), an anticholinergic drug, was given to the dogs of above groups before the administration of imidocarb dipropionate. An interval of four weeks was kept between this and above experiments. Alterations, if any, in the behavioural response of dogs were observed.

RESULTS AND DISCUSSION

Plasma cholinesterase (ChE) and erythrocyte acetylcholinesterase (AChE) at different time intervals following i/v and i/m administration of imidocarb dipropionate were estimated immediately after collection of blood samples. Results were expressed as μ mole of thiocholine produced per 10 min (Table). Imidocarb dipropionate on intravenous administration sharply decreased ChE activity from a normal of 0.118 (μ mole of thiocholine produced per 10 min) to a minimum of 0.042 (36 %) at 1 h. Thereafter, ChE activity recovered to about 80 per cent of the normal in 24 h. The AChE activity also decreased from a normal of 0.13 to 0.08 (61.5 %) at 4 to 6 h and recovered to the extent of about 84 per cent of the normal in 24 h.

Imidocarb dipropionate given by intramuscular route at same dose rate also decreased the activities of both ChE and AChE. As compared to normal activity of ChE of 0.115, the enzyme activity decreased to a low of 0.076 (66 %) at 4 h. Similarly, AChE was decreased from normal of 0.13 to 0.109 (84 %) at 4 h. ChE and AChE activity returned to about 95 per cent of the normal in 24 h. The inhibition of activity of both ChE and AChE were appreciable after administration of imidocarb dipropionate through i/v and i/m routes.

The cholinergic symptoms like profuse salivation, restlessness, lacrimation, frequent defecation, fasciculation, respiratory distress and panting appeared within two min of intravenous administration (6.5 mg kg⁻¹) and lasted up to two hours after i/v administration of imidocarb dipropionate. On intramuscular administration the same symptoms appeared after 5-10 min. Atropine sulphate at the dose rate of 0.01 mg.kg⁻¹, i/v completely blocked the gross symptoms when imidocarb was administered intramuscularly and symptoms appeared for half an hour when imidocarb was administered intravenously.

Imidocarb, on single intravenous or intramuscular administration, decreased rapidly the ChE and AChE activity in dogs.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Intravenous route</th>
<th>Intramuscular route</th>
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<tbody>
<tr>
<td></td>
<td>ChE</td>
<td>AChE</td>
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<tr>
<td>0</td>
<td>0.118±0.002</td>
<td>0.130±0.003</td>
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<tr>
<td>1/4</td>
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<td>0.125±0.002</td>
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<tr>
<td>1/2</td>
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<td>0.119±0.002</td>
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<tr>
<td>1</td>
<td>0.042±0.002</td>
<td>0.112±0.001</td>
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<tr>
<td>2</td>
<td>0.051±0.003</td>
<td>0.098±0.002</td>
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<tr>
<td>4</td>
<td>0.067±0.003</td>
<td>0.081±0.002</td>
</tr>
<tr>
<td>6</td>
<td>0.075±0.002</td>
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<tr>
<td>9</td>
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<td>0.089±0.002</td>
<td>0.099±0.002</td>
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<tr>
<td>24</td>
<td>0.094±0.002</td>
<td>0.118±0.002</td>
</tr>
</tbody>
</table>

Values are mean±S.E. of five animals.
activities in dogs. The extent of inhibition of ChE and AChE activities was early and higher on intravenous than intramuscular administration. The inhibition of cholinesterase activity might have resulted into increased acetylcholine level, consequently, mild to severe cholinergic symptoms appeared in dogs. The duration of cholinergic symptoms was almost coincidental with the duration of inhibition of cholinesterase activity both on intravenous or intramuscular administration of imidocarb dipropionate. Todorovic et al. (1973) also observed cholinergic symptoms in calves exhibiting dyspnoea, gasping, excessive salivation, muscular fasciculations, incoordination, prostration and even death in some calves on intravenous administration. The signs of toxicosis were milder after intramuscular administration of imidocarb dipropionate. The inhibition of cholinesterase activity as observed in present study supports the cause of toxic cholinomimetic effects of imidocarb dipropionate. Corrier (1975) also observed toxic and clinical signs of excessive salivation, diarrhoea and dyspnoea followed by coma and deaths in goats. Studies conducted by Adams et al. (1980) on toxicity of imidocarb dipropionate in cattle can be related to anticholinesterase activity, since the observed symptoms like excessive salivation, serous nasal discharge, diarrhoea and dyspnoea were cholinergic in nature. In calves, whole blood cholinesterase activities were significantly reduced following intramuscular injection of imidocarb dipropionate. While conducting pharmacokinetic studies, Abdullah et al. (1984) observed adverse cholinergic effects of imidocarb dipropionate in dogs. On intravenous administration, there was transient salivation and diarrhoea immediately after injection. Difficulty in breathing, tachycardia, weakness and profuse diarrhoea were followed by death in some cases. The inhibition of cholinesterase activity in present study also supported the observation of Singh et al. (1990) in male goats treated with imidocarb dipropionate, who observed transient salivation and lacrimation. Rao et al. (1980) has also observed that imidocarb produced hypotensive action in anaesthetized dogs and also potentiated the hypotensive action of acetylcholine, which was blocked by atropine. They also observed imidocarb potentiated acetylcholine induced contractions of guinea pig ileum, which was antagonized by atropine. Prior treatment of dogs with atropine (0.01 mg/kg, i/v) in this study have been found to block the clinical signs of toxicity when imidocarb was administered by intramuscular route. However, at this dose level atropine significantly reduced the severity of clinical signs of imidocarb given intravenously. From these studies, it can be speculated that the clinical or toxic cholinergic signs may be due to cholinomimetic effects of imidocarb dipropionate as a result of inhibition of erythrocyte acetylcholinesterase and plasma cholinesterase activities which could be blocked or reduced by prior administration of atropine sulphate.

REFERENCES


