ANTIPYRETIC ACTIVITY OF DIACETYL PARA-AMINO PHENOL

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Abstract: Diacetyl para-amino phenol (DAPAP) was generated by interaction between aspirin and paracetamol in a mechanical shaker. It revealed antipyretic activity in albino rats. The antipyretic action was found to be having the same onset of action and duration as that of aspirin. This compound lacked ulcerogenic and analgesic activity. DAPAP therefore may have safety as an antipyretic drug in patients with history of peptic ulcer.

Key words: diacetyl para-aminophenol ulcerogenic antipyretic and analgesic

INTRODUCTION

Although, it is generally believed that the interaction between aspirin and paracetamol leading to the formation of diacetyl para amino phenol (DAPAP) (1) does not cause loss of therapeutic activity of aspirin, one may expect the compound to be either more or less active than the reactants. Hence, it was thought worthwhile to evaluate DAPAP for antipyretic and ulcerogenic activity in rats.

Preparation and isolation of DAPAP: A 50:50 v/v mixture of methanol and distilled water was employed for the preparation of saturated solutions of aspirin and paracetamol. They were placed in a round bottom flask (ratio of aspirin and paracetamol, 7:3). To this was added equal quantity of 20 ml each of acetic anhydride and analytical grade pyridine. This mixture was refluxed on an electrical water bath for three hr and cooled. On cooling yellowish brown crystals appeared. They were recrystallised in methanol and treated with activated charcoal to give brilliant white crystals of DAPAP (1).

Antipyretic activity: Both acute antipyretic potency and the duration of antipyresis of the interaction product, DAPAP were studied (2) on albino rats. The normal rectal temperature of albino rats of either sex (10-15 g) were recorded for 8 hr. Pyrexia was induced by the dorsal and ventral subcutaneous administration of two 1 ml quantities of 44% yeast suspension (0.6 ounce cake of Fleischmann's Baker's yeast in 22 ml of 0.9% sodium chloride). The site of injection was then massaged again to stimulate a further increase in body temperature. At 18th hr the rectal temperature was recorded for the second time, using rectal thermometer. This temperature served as the base line temperature from which antipyresis was determined.

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The drug was then administered orally as an aqueous suspension made with two drops of Tween 80. Control rats were given saline by the same route. Aspirin and paracetamol were used as standard controls.

For the determination of antipyresis the temperature was noted hourly until 6.5 hr after drug administration.

**Uleerogenic activity:** The acute ulcerogenic or gastric mucosal eroding effect of DAPAP was evaluated by modification of the method reported by Hitchens et al. (3). Albino rats of either sex (110-140 g) were starved for 18 hr but given water ad libitum.

A group of 6 rats was kept as control, and to groups of 6 rats each, aspirin DAPAP and paracetamol (doses 150, 160 and 135 mg/kg, respectively) were administered orally. The control groups received 2 ml of 0.5% acacia with 2 drops of Tween 80. Four hr later the animals were sacrificed. The stomach was removed, washed and fixed in 10% formalin. Stomachs were cut along the greater curvature, mounted on flat surface and photographed. They were examined for the presence of eroded or ulcerated areas. Ulcers were scored (4) and ulcer index was thus, calculated.

### RESULTS AND DISCUSSION

Using Student's t-test observations in Table I indicate that DAPAP exhibits significant (P<0.01) antipyretic effect for a duration of 5 hr.

The ulcer index was found to be 4 for aspirin and 0 for DAPAP which shows that DAPAP is devoid of ulcerogenic activity, though ED 50's were found to be comparable (6).

#### TABLE I: Comparative study of antipyretic activity of aspirin DAPAP and paracetamol in rats treated with 1 ml of 4% yeast suspensions.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Dose (mg/kg orally)</th>
<th>Initial rise</th>
<th>Rectal temperature (Mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>1.</td>
<td>Control</td>
<td>—</td>
<td>2.5±0.21</td>
<td>2.2±0.1</td>
</tr>
<tr>
<td>2.</td>
<td>Aspirin</td>
<td>150</td>
<td>2.3±0.23</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>3.</td>
<td>DAPAP</td>
<td>160</td>
<td>2.5±0.23</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>4.</td>
<td>Paracetamol</td>
<td>125</td>
<td>3.0±0.3</td>
<td>1.0±0.1</td>
</tr>
</tbody>
</table>

n=6 in each group
The percentage protection DAPAP gives against writhing is 3.82 which is negligible when compared to aspirin (Table II).

These studies show that DAPAP can be used as a potent, safe and effective antipyretic drug as it is devoid ulcerogenic action.

### TABLE II: Comparative protection offered by aspirin, DAPAP and paracetamol against acute acid induced of withing in mice.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Dose mg/kg (oral)</th>
<th>Number of writhings</th>
<th>Percentage protection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Average</td>
</tr>
<tr>
<td>1.</td>
<td>Control</td>
<td>—</td>
<td>141</td>
<td>23.5</td>
</tr>
<tr>
<td>2.</td>
<td>Aspirin</td>
<td>165</td>
<td>20</td>
<td>3.33</td>
</tr>
<tr>
<td>3.</td>
<td>DAPAP</td>
<td>175</td>
<td>196</td>
<td>22.6</td>
</tr>
<tr>
<td>4.</td>
<td>Paracetamol</td>
<td>135</td>
<td>22</td>
<td>3.6</td>
</tr>
</tbody>
</table>

n=6 in each group

### REFERENCES


