INFRAADDITIVE DIURETIC EFFICACY OF CONCURRENT AMINOPHYLLINE AND FRUSEMIDE

S. K. TONGIA,* S. P. DHANERIA AND P. NYATI

Department of Pharmacology,
M.G.M Medical College,
Indore - 452 001 (M.P.)

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Abstract: Male albino rats weighing between 150-225 gm fasted over night but freed having water ad libitum were used to assess the diuretic efficacy of intramuscular aminophylline and frusemide separately and concurrently after intraperitoneal 10 ml of distilled water loading. The normal rate of diuretic weight loss was less augmented by aminophylline and more augmented by frusemide. The diuretic response was more by the concurrent intramuscular administration of aminophylline and frusemide in comparison with that due to either drug alone. However, the observed diuretic response of the two drugs administered concurrently was lesser (infraadditive) than the sum of the individual diuretic response (additive).

Key words: diuretic diuretic efficacy diuretic weight loss aminophylline frusemide

INTRODUCTION

Quite often aminophylline and frusemide are used concomitently in cardiac failure and pulmonary oedema, the former for its cardiac stimulatory, vasodilator, bronchodilator and diuretic (1) and the later for its diuretic activiy (2, 3) in the complex clinical situation (4). The net duretic effect emerging from the administration of aminophylline and frusemide concurrently has not been reported (5). The present work is therefore planned to investigate the diuretic efficacy of the two best drugs in combination.

METHODS

A total of 40 albino male rats (weighing between 150-225 gm.) were divided into 4 groups of 10 each and kept individually in cages at 25°C. The animals were fasted, but water was allowed ad libitum, for 20 hours before use. Each rat was weighted and then loaded up with 10 ml of distilled water i.p. The animal again weighed after the injection. There was an increase by 10 gm in the body weight at 0 min. The rat was weighed every 15 min. The rapid rate of reduction in body weight which followed, was the indicator of the rate of urine voided. The rats of the group 1 were loaded only with distilled water which served as normal control. Those of second group were injected aminophylline 2.5 mg/kg of body weight im 10 min before water loading. Those of the third group were injected frusemide 2.5 mg/kg of body weight im and those of the fourth group were injected aminophylline 3.5 mg per kg of body weight im in the right thigh and frusemide 2.5 mg/kg of body weight im in the left thigh 10 min before the water loading. The rate of diuretic weight loss was recorded as values cumulative with time.

RESULTS

The Table I and Fig.1 show that the weight loss increases with aminophylline and frusemide respectively though the response was more with the later drug.

Aminophylline caused 45%, 55% and 69% loss of loaded water in 15, 30 and 45 min respectively whereas the corresponding figures for frusemide are 58%, 65% and 85%. In concert of aminophylline and frusemide the rate of diuretic weight loss observed was 58%, 75% and 101% of the loaded water in 15, 30 and 45 min interval of time. Thus there was a reduction...
DISCUSSION

The result of this study demonstrate the suppressive effect of cimetidine on gonadotrophs. Decreased secretory granules as indicated by low stained hypotrophied gonadotrophs and reduced cell population and cell volume indicated this effect. Studies have demonstrated that administration of testosterone suppresses the secretion of pituitary gonadotrophins (8,9). Recently it has been shown that cimetidine causes hypertrophy of Leydig cells and seminiferous epithelium of testis (3) and serum testosterone increases with the increase in the number & size of Leydig cells (10,11). Hence the observed suppressive of cimetidine on gonadotrophs of pituitary gland is due to increased production of testosterone from hypertrophied Leydig cells rather then it’s direct effect on adenohypophysis.

Bilateral orchidectomy in mice causes significant hypertrophy & hyperplasia of gonadotrophs (both LH and FSH cells) and lactotrophs which is due to lack of testosterone as there is total removal of testis. Administration of cimetidine to orchidectomyed mice does not bring about any significant change in the gonadotrophs as observed in group 5. This is due to fact that the effect of cimetidine on pituitary gonadotrophs is mediated through the testis. Since the testes were removed “Cimetidine-testis-pituitary gland” cycle was broken.

It can be argued that administration of cimetidine to male albino mice can suppress the pituitary gonadotrophs through the secretion of testosterone from hypertrophied Leydig cells of testis.

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REFERENCES

1. Rudder WSJ, Reed DI, Hill MJ, Taylor TV. Gastric cancer who have taken cimetidine. Lancet 1979; 2: 1234-1236.
of 45%, 45% and 50% in the diuretic weight loss at 15, 30 and 45 min intervals respectively with the concert of aminophylline and frusemide as compared to the additive response of the two drugs administered separately. The observation is indicative of infradditive diuretic response of aminophylline and frusemide if used concomittantly.

**DISCUSSION**

Aminophylline and frusemide remove body water by causing diuresis through different mechanisms, the former by causing renal vasodilatation and increasing renal blood flow (1, 4) and the later by inhibiting salt and water reabsorption in the loop of Henle (2, 3, 4). It seems that if the two agents acting by different mechanisms for diuresis are combined, they should predictably act in synergism for additive or supraadditive (potentiation) effect (5). Contrary to our prediction, the present study has demonstrated an infradditive diuretic response following concurrant administration of aminophylline and frusemide. Previously (6) reported that no additional diuretic effect is produced by frusemide over the response of aminophylline administered in the dose of 3.5 mg/kg intravenously. This could be due to the dose of 3.5 mg/kg and intravenous route of aminophylline which produced maximal diuresis. Therefore in the present study the dose of aminophylline was decreased by 1/3 to 2.5 mg/kg and the route was changed to intramuscular with the object of determining additive, supraadditive or infradditive diuretic response with concurrent

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 min</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>75 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Control</td>
<td>0.00</td>
<td>4.18±1.26</td>
<td>4.25±1.78</td>
<td>6.15±1.17</td>
<td>6.63±1.41</td>
<td>8.25±1.5</td>
<td>9.55±1.58</td>
</tr>
<tr>
<td>A. Aminophylline</td>
<td>2.5 mg/kg</td>
<td>4.52±1.46</td>
<td>5.03±1.15</td>
<td>7.4±1.47</td>
<td>8.28±1.87</td>
<td>9.5±2.23</td>
<td>10.32±2.15</td>
</tr>
<tr>
<td>F. Frusemide 2.5 mg/kg</td>
<td>5.85±1.22</td>
<td>6.57±0.66</td>
<td>9.15±2.2</td>
<td>10.19±2.69</td>
<td>11.25±2.84</td>
<td>12.03±2.49</td>
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</tr>
<tr>
<td>A+F Aminophylline</td>
<td>2.5 mg/kg</td>
<td>5.8±1.09</td>
<td>7.5±2</td>
<td>10.05±2.66</td>
<td>11.99±2.65</td>
<td>11.87±2.58</td>
<td>12.3±3.15</td>
</tr>
<tr>
<td>Expected for additive effect of Aminophylline and Frusemide</td>
<td>10.37±1.34</td>
<td>11.2±0.9</td>
<td>16.5±1.8</td>
<td>18.47±2.2</td>
<td>20.7±2.5</td>
<td>22.37±2.2</td>
<td></td>
</tr>
</tbody>
</table>

P Value varied between <0.05 to >0.01 on comparison between groups - C vs A, C vs F, C vs A+F
aminophylline and frusemide administration. Intramuscular aminophylline per se being painful, so highly diluted aminophylline was used for the initial trial experiment in the albino rats.

The study registers its importance in complex clinical situation inviting the use of aminophylline for its cardiorespiratory attributes and frusemide for its diuretic virtue, since the diuretic efficacy of frusemide is decreased. The phenomenon apparently appears to be one of antagonism of mutual diuretic response. The mechanism of infra-additive diuretic efficacy needs exploration.

REFERENCES


