

INFRAADDITIVE DIURETIC EFFICACY OF CONCURRENT AMINOPHYLLINE AND FRUSEMIDE

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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 concomitantly in cardiac failure and pulmonary oedema, the former for its cardiac stimulatory, vasodilator, bronchodilator and diuretic (1) and the later for its diuretic activity (2, 3) in the complex clinical situation (4). The net diuretic 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 weighed 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 I 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

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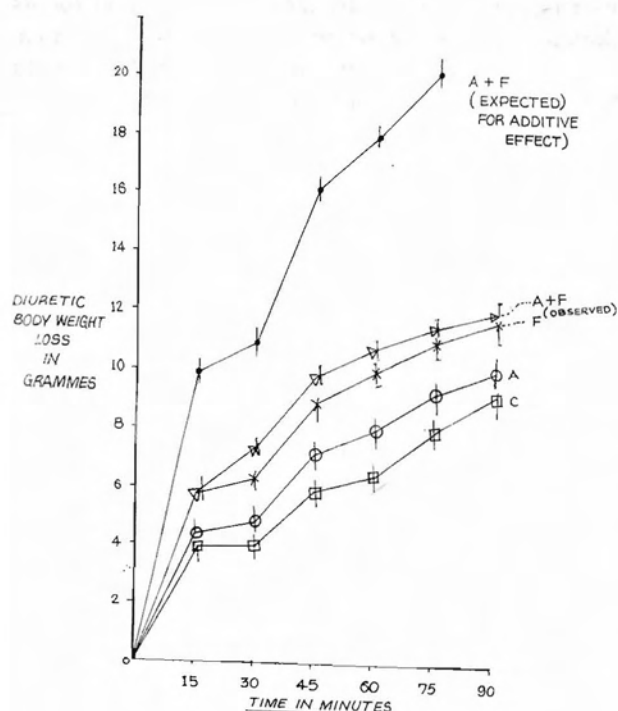


Fig. 1: Diuretic body weight loss. Response in albino rats after 10 ml, i.p. water loading under control C and treatment with drugs -

A- aminophylline 2.5 mg/kg, im. $\circ-\circ$, F-Frusemide 2.5 mg/kg im $\times-\times$ A+F (observed) $\triangle-\triangle$, A+F (Expected for Additive Effect) $\bullet-\bullet$ Each point represent the mean of 10 observations and vertical bars, standard error of mean (SEM).

P values varies between <0.06 to >0.01 on comparison of groups- C vs A, C vs F, C vs A+F

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 infraadditive diuretic response of aminophylline and frusemide if used concomitantly.

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 infraadditive diuretic response following concurrent administration of aminophylline and frusemide. Previously (6) is 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 infraadditive diuretic response with concurrent

TABLE I: Showing diuretic weight loss in grammes \pm SEM in rats under treatments.

Groups		Diuretic weight loss in gramme \pm SEM						
		0 min	15 min	30 min	45 min	60 min	75 min	90 min
C.	Control (water loading 10 ml, i.p.)	0	4.18 \pm 1.26	4.25 \pm 1.78	6.15 \pm 1.17	6.63 \pm 1.41	8.25 \pm 1.5	9.55 \pm 1.58
A.	Aminophylline 2.5 mg/kg im + Water loading 10 ml, i.p.	0	4.52 \pm 1.46	5.03 \pm 1.15	7.4 \pm 1.47	8.28 \pm 1.87	9.5 \pm 2.23	10.32 \pm 2.15
F.	Frusemide 2.5 mg/kg im + Water loading 10 ml, i.p.	0	5.85 \pm 1.22	6.57 \pm .66	9.15 \pm 2.2	10.19 \pm 2.69	11.25 \pm 2.84	12.03 \pm 2.49
A+F	Aminophylline 2.5 mg/kg im + Frusemide 2.5 mg/kg im + Water loading 10 ml, ip.	0	5.8 \pm 1.09	7.5 \pm 2	10.05 \pm 2.66	11.99 \pm 2.65	11.87 \pm 2.58	12.3 \pm 3.15
	Expected for additive effect of Aminophylline and Frusemide	0	10.37 \pm 13.4	11.2 \pm 0.9	16.5 \pm 1.8	18.47 \pm 2.2	20.7 \pm 2.5	22.37 \pm 2.2

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.

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