SUMMARY
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Development of resistance to loop diuretic is a common clinical phenomenon. Virtually all patients with edematous disorder manifest some element of diuretic resistance.

The present study was designed to evaluate the effect of chronic dosing of hydrochlorothiazide (50mg) plus furosemide (40mg) and spironolactone (50mg) plus furosemide (40mg) in comparison to furosemide (40mg), furosemide (80 mg), hydrochlorothiazide (50 mg), spironolactone (50 mg) and placebo on electrolytes, urine volume, body weight and arterial blood pressure in healthy human subjects. The objective was to develop a model, which gives an insight of the mechanism of development of resistance and hence helps in optimizing the therapy on that basis.

In order to validate the phenomenon of development of diuretic resistance in healthy human volunteers, a pilot study was conducted with the furosemide 40 mg administered over a period of five days. There was significant decrease in urine volume and urinary sodium output when furosemide 40 mg was administered over a period of five days. However there was no change in potassium output when furosemide was given repeated for five days. This methodology was used in the definitive study with furosemide administration for five days.

The definitive study was randomised, single blind, crossover, placebo controlled, seven treatment, seven period, multiple dose pharmacodynamic study. The primary objective of the study was to evaluate in healthy subject, the multiple dose effects of furosemide (40mg) plus hydrochlorothiazide (50mg) and furosemide (40mg) plus spironolactone (50mg) combinations in comparison to furosemide (40mg), furosemide (80mg) hydrochlorothiazide (50mg), spironolactone (50 mg) and placebo on the electrolytes and urinary volume.
The secondary objective of the study was to evaluate the effect of above-mentioned interventions on the body weight and arterial blood pressure if any. The study was performed as per the protocol 01 / JamHam /02 using ICH : GCP 1996 Guidelines. Urine collection was by spontaneous voiding on Day1 and Day5. Collection of urine was done at predetermined interval for twelve hours. The randomisation sheet was generated using SAS, a statistical software. Out of fourteen subjects, one subject was withdrawn from the study in the seventh period on ethical grounds and one subject dropped out of the trial after first visit in the first period. No drug related adverse event was reported / observed. All subject met the compliance criteria.

There was significant decrease in urine volume and urinary sodium output with both the doses of furosemide 40 mg and 80 mg when administered over a period of five days. However there was no change in potassium output when furosemide 40 mg was given repeated for five days. Both the combination diuretic therapy showed a trend in conservation in water but loss in sodium. Combination of hydrochlorothiazide 50 mg with furosemide 80 mg doesn't showed the additive diuretic response in comparison to situation when given individually. However, in case of spironolactone 50 mg combination with furosemide 40 mg diuresis was maintained over a period of five days treatment.

The result obtained have been discussed. It was concluded that repeated dose of furosemide (once daily for five days) causes significant reduction in urine volume and urinary electrolyte and thereby leads to development of resistance, which is dose proportional in healthy human volunteer. Combination of furosemide with diuretic, which is an antagonist of aldosterone like spironolactone, counteracted the development of resistance. However, replication of this study in normal volunteer admitted in metabolic unit is warranted to reduce large intersubject variability associated with this outpatient based study.