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BIOAVAILABILITY OF TWO FRUSEMIDE PREPARATIONS

It has been shown that the bioavailability of the diuretic frusemide as Lasix tablets is similar to that of the drug given as a water solution (Kelly, Cutler, Forrey & Kimpel, 1974).

There are at least two marketed brands of frusemide, Impugan and Lasix. No paper has been published which compares the bioavailability of those two preparations.

Five healthy male subjects volunteered for the investigation. Their age ranged between 25 and 29 years. They were healthy according to history, physical examination and laboratory tests (Hb, WBC, thrombocytes, ESR, S-ALAT, S-ASAT, creatinine clearance and S-electrolytes i.e. Na⁺, K⁺, Ca⁺⁺ and Mg⁺⁺). The subjects were asked to refrain from the use of alcohol and heavy physical strain during 3 days before every test day.

Each subject took part in three experiments at least 1 week apart in a randomized order. They were given at 08.00 h (time 0) (a) placebo, (b) 40 mg frusemide as Impugan (A/S Dumex, Copenhagen, Denmark) or (c) 40 mg frusemide as Lasix (Hoechst AG, Frankfurt (M), FRG), after fasting overnight.

The subjects were given tap water (150 ml) each hour from 2 to 10 h except at 4, 5 and 6 h, when 75 ml of the tap water was replaced by Trilgar (carbohydrates 0.53 g ml⁻¹, Na⁺ 30 µmol ml⁻¹, K⁺ 0.8 µmol ml⁻¹, Ca⁺⁺ 1, 5 µmol ml⁻¹, Mg⁺⁺ 2.5 µmol ml⁻¹, Cl⁻ 8.5 µmol ml⁻¹ and PO₄³⁻ 6.3 µmol ml⁻¹). After 10 h the subjects were permitted to drink, eat and smoke.

Venous blood samples were collected at 15, 30, 45, 60, 90, 120 and 150 min and thereafter at each h to 12 h. After centrifugation, plasma was stored at -20°C until analysis. The subjects emptied their bladders immediately before the start of the experiment. The urine was collected every 0.5 h until 4 h, thereafter hourly until 10 h.

The concentrations of frusemide in plasma and

urine were determined with GLC (Lindström & Molander, 1974) and HPLC (Lindström, 1974) respectively. The GLC assay was used with a modification: 1% Se 30 column (1 m) operated at 220°C, injector temp 230°C, detector temp 300°C. Each series of plasma and urine specimens was analyzed on the same occasion.

The urine specimen was analyzed for its Na⁺ and K⁺ content by flame photometry (Flamephotometer 3 L 143, Instrumentation Inc.) and those of Ca⁺⁺ and Mg⁺⁺ by atomic absorption spectrophotometry (Perkin-Elmer 306) at the Department of Clinical Chemistry at Serafimerlasarettet.

The area under the plasma concentration time curve was calculated by the trapezoidal rule and extrapolated to infinity (AUC_{0-∞}) from the last measurable plasma concentration (> 10 ng ml⁻¹).

Statistical comparisons were made with Student's paired *t*-test. Averages are presented as mean ± 1 s.d.

After administration of 40 mg Impugan, maximal plasma levels were seen at 0.80 ± 0.33 h on average and they amounted to 2079 ± 540 ng ml⁻¹. The corresponding figures after 40 mg Lasix were 1.75 ± 1.22 h and 1836 ± 800 ng ml⁻¹ respectively. Although the peaks after Lasix tended to be less high and to appear later than after Impugan, the differences were not significant. AUC_{0-∞} after Impugan and Lasix averaged 3044 ± 763 and 3193 ± 760 ng ml⁻¹ h respectively (NS).

The urinary recovery of frusemide during 10 h after 40 mg Impugan amounted to 16.5 ± 4.4 mg in mean and that after Lasix to 18.2 ± 6.0 mg (NS).

The diuresis during the first 6 h after 40 mg Impugan was on average 1084 ± 395 ml higher than after placebo. The corresponding figure after Lasix was 987 ± 127 ml (NS). Likewise there was no significant difference between the increases in urinary excretion of Na⁺ (135 ± 51, 133 ± 25 mmol) K⁺ (20 ± 14, 22 ± 11 mmol) Ca⁺⁺ (1.02 ± 0.87,

1.63 $\pm$ 0.43 mmol) and Mg⁺⁺ (0.70 $\pm$ 0.50, 0.84 $\pm$ 0.34 mmol) obtained after administration of Impugan and Lasix respectively.

Comparisons between the bioavailability of synonymous drug preparations can be based on plasma levels and urinary recovery of the drug or on effects of the compounds in single or multiple dose regimens.

Chronic treatment of healthy volunteers with frusemide would be rather inconvenient to the subjects. Thus we chose a single-dose design with measurement of several pharmacokinetic and pharmacodynamic parameters.

The time of the peak levels of frusemide did not differ significantly between Impugan and Lasix. The similarities in the area under plasma concentration time curves and in the urinary recovery after oral administration of Impugan and Lasix indicate that the two preparations do not differ in bioavailability.

When comparing the bioavailability of a compound with pharmacodynamic parameters, it is essential that the dose given is on the steep part of the dose response curve. This prerequisite is fulfilled for a 40 mg dose of frusemide (Kleinfelder, 1963). Thus the similarity in the diuretic response and in the increase in electrolyte excretion after 40 mg frusemide as Impugan and Lasix strongly supports the view that the two brands of frusemide are generically equivalent.

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PLATELET AGGREGATION AND CHLORPROMAZINE THERAPY

Recently we have attempted to replicate earlier data showing enhancement of 5-HT induced aggregation of platelets from patients taking chlorpromazine (CPZ). Twenty-two tests have been made in fourteen patients and in only one case has enhancement been observed. In this recent study the patients came from another mental hospital, but as far as we are aware there are no methodological problems which could account for the failure to repeat the earlier observations. Enhancement is still being observed in some of the patients involved in the original study of 1974/5 (Boullin, Woods, Grimes, Grahame-Smith, Wiles, Gelder, & Kolakowska, 1975; Boullin & Grimes, 1976).

Table 1 compares the recent observations with those of the 1974/5 study. It is quite clear that 5-HT aggregation responses are normal. On the other hand

Table 2 shows that plasma CPZ was quite high in eight of the fourteen subjects studied now; plasma CPZ was measured in only three subjects in the original investigation.

At an international meeting concerned with the pharmacology of platelets, held in Florence in September, 1977, Boullin, Orr & Peters reported that 25 out of 34 patients showed enhancement of 5-HT induced aggregation. They suggested the phenomenon might have value as a predictive test for treatment of schizophrenics. The proceedings of the meeting in which those views were expressed are in press (Boullin, Orr & Peters, 1978). Accordingly it is necessary for us to publish the new results and to state that the views expressed earlier will need re-evaluation. Although platelet aggregation responses to 5-HT may have some predictive value in the CPZ treatment of