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BIOAVAILABILITY AND DISPOSITION OF METOPROLOL AND HYDROCHLOROTHIAZIDE COMBINED IN ONE TABLET AND OF SEPARATE DOSES OF HYDROCHLOROTHIAZIDE

L. JORDÖ*, G. JOHNSSON, P. LUNDBORG, B.A. PERSSON, C.-G. REGÅRDH & O. RÖNN

Department of Medicine II, Sahlgren's Hospital, 413 45 Gothenburg, Sweden and and Research Laboratories, AB Hässle, Mölndal, Sweden

1 The plasma levels and the urinary excretion of hydrochlorothiazide (HCT) have been studied after administration of single doses of 12.5 and 25 mg of the drug in solution and in combination with 100 mg of the selective β_1-adrenoreceptor antagonist metoprolol in a rapidly dissolving tablet.

2 Metoprolol did not significantly influence the bioavailability or the time-course of HCT.

3 HCT had no significant effect on the time-course or the plasma levels of metoprolol. The average half-life, 4.4 ± 0.9 h, is about the same as previously observed for separate doses of this drug.

4 It seems unlikely that repeated doses of the combination product studied will lead to biopharmaceutic or pharmacokinetic interactions of clinical importance.

Introduction

It has been estimated that about 60% of an unselected population of hypertensive patients will have their blood pressure effectively controlled by a β-adrenoreceptor blocking agent alone (Hansson, 1976). A substantial increase in the number of responders has been obtained when various β-adrenoceptor antagonists have been combined with saluretics (O'Brien & MacKinnen, 1972; Castenfors, Johnsson & Orö, 1973; Chalmers, Korner, Tiller, Bune, Steiner, West, Wing & Uther, 1976; Chalmbers, Tiller, Horvatt & Bune, 1976; Jäättelä & Pyörälä, 1976; Lancaster, Goodwin & Peart, 1976).

In these studies the drugs have been given separately. This increases the daily number of doses the patients have to ingest which may lead to reduced compliance (Gately, 1968). One way to avoid this might be to combine the drugs into one single tablet provided that the biopharmaceutical properties of the individual drugs are not affected.

In addition to dosage form related interactions that might lead to changes in the bioavailability of the two drugs, interactions may also occur pharmacodynamically and pharmacokinetically. Thus, the haemodynamic effects of the β-adrenoreceptor antagonists – primarily the reduction of cardiac output – might influence the rate of absorption, distribution and elimination of hydrochlorothiazide (HCT) by changing the splanchnic blood flow and the perfusion of various extravascular tissues including the kidneys through which HCT is almost exclusively eliminated from the body. On the other hand, it is also plausible that the reduction of the plasma volume associated with the diuretic effect of HCT would result in increased plasma levels of the β-adrenoceptor antagonists.

The present study has been carried out to investigate the pharmacokinetic and biopharmaceutic properties of the selective β_1-adrenoceptor antagonist metoprolol and HCT simultaneously administered in one single tablet.

Methods

Design of the study

Single HCT doses of 12.5 and 25 mg were administered separately and in combination with 100 mg metoprolol to six healthy volunteers who consented to participate after having received full information about the purpose of the study. The study was approved by the local ethical committee at the University of Gothenburg. The doses were given in randomized order at least 1 week apart. The experiments were started at 08.00 h after the subjects

*Present address: Medical Department, Central Hospital, S-431 80 Mölndal, Sweden

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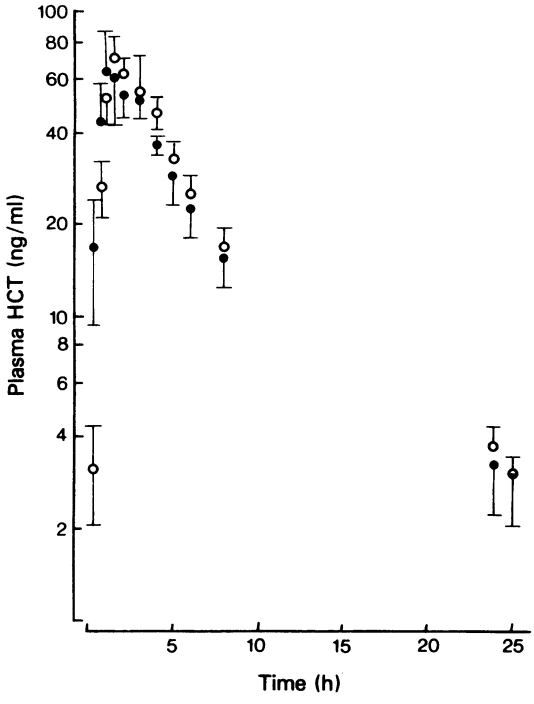

Figure 1 Mean and s.e. mean ($n=6$) plasma concentrations of hydrochlorothiazide (HCT) after administration of 12.5 mg in solution (●) and in combination with 100 mg (O) metoprolol in a rapidly dissolving tablet.

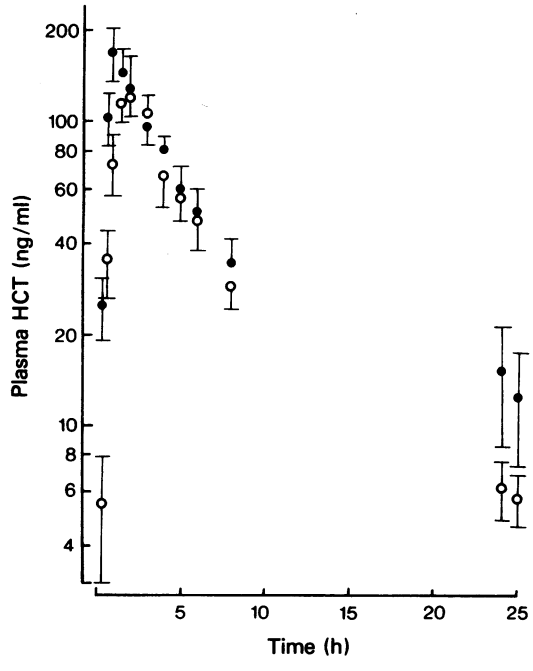

Figure 2 Mean and s.e. mean ($n=6$) plasma concentration of hydrochlorothiazide (HCT) after administration of 25 mg in solution (●) and in combination with 100 mg (O) metoprolol in a rapidly dissolving tablet.

had fasted for at least 10 h. No food was allowed until 3 h after the administration and the intake of food was then standardized for the next 5 h. A blank blood sample was drawn prior to the administration. Blood (10 ml) was thereafter collected in heparinized test tubes at convenient intervals for the total of 25 h. After centrifugation the plasma was stored at −20°C until analysis. Urine was collected quantitatively for 48 h and the amount of HCT excreted was determined. The urine specimens were stored deep-frozen until analysis.

Analysis of metoprolol and hydrochlorothiazide in plasma and urine

Both metoprolol and HCT were assayed by gas-liquid chromatography and electron capture detection, metoprolol after trifluoroacetylation (Ervik, 1975) and HCT after extractive alkylation (Lindström, Molander & Groschinsky-Grind, 1976).

Preparations

The 12.5 and 25 mg doses of HCT were administered dissolved in 50 ml of an alcoholic solution (20%). The bottles containing the solution were rinsed twice with 25 ml water which was ingested together with the drug solution.

The combined HCT-metoprolol dose was a rapidly dissolving tablet based on the formulation of the 100 mg metoprolol tartrate tablet (Seloken®, AB Hässle, Sweden). Metoprolol was completely dissolved from this tablet within 30 min and > 80% of the HCT dose was dissolved within 60 min when tested according to the rotating basket method of USP XVIII, 100 rev/min. The tablets were administered together with 100 ml water.

Results

Hydrochlorothiazide

The average plasma concentrations of HCT after administration of 12.5 and 25 mg of the drug alone and in combination with 100 mg metoprolol are shown in Figures 1 and 2. The pharmacokinetic parameters derived from the individual plasma concentration data are summarized in Table I. According to this table the area under the curve, AUC_{25}, was about 450 ng h ml^{-1} for the 12.5 mg dose and increased about twofold when the HCT dose was

doubled. Similarly, the mean peak plasma levels, $C_{p,max}$, which were about 75 ng/ml for the low dose, were increased about twice. Neither of these two parameters was affected by concomitant administration of metoprolol, nor did the β-adrenoceptor antagonist influence the half-life $T_{\frac{1}{2}}$, of the diuretic between 2 to 8 h after the administration, Table 1 (see discussion). The only parameter that was changed by the incorporation of HCT in the 100 mg metoprolol tablet was the time to reach the maximum concentration, t_{max}, of the 25 mg HCT dose. Thus, t_{max} of the solution was 1.3 ± 0.2 h and 2.2 ± 0.3 h after ingestion of the tablet ($P < 0.05$).

On the average 60 to 73% of the administered HCT dose was excreted in unchanged form via the kidneys during 48 h, Table 2. Inter-individually, the recovery ranged between 39 and 96%.

Metoprolol

The average plasma concentrations of metoprolol after administration of the drug together with 12.5 and 25 mg HCT, respectively, are shown in Figure 3. The time to reach the maximum concentration was 1.0 ± 0.1 when metoprolol was administered together with 12.5 mg HCT and 1.5 ± 0.2 h for the other combination. The corresponding maximum concentrations were 167 ± 34 ng/ml and 133 ± 27 ng/ml.

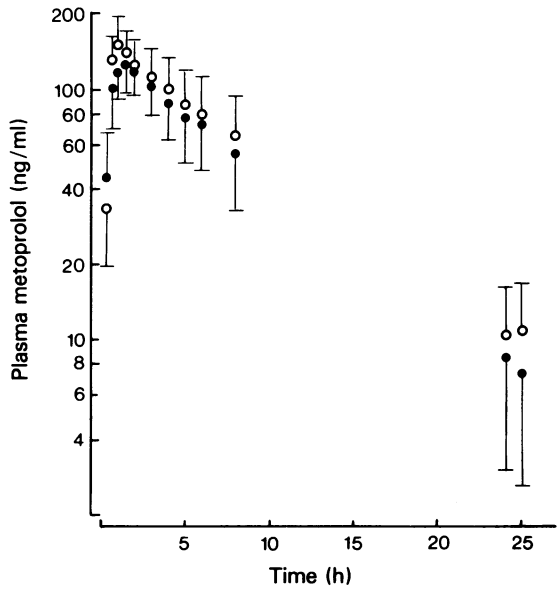

Figure 3 Mean and s.e. mean ($n = 6$) plasma concentrations of metoprolol after administration of 100 mg of the drug in combination with 12.5 mg (●) and 25 mg (○) hydrochlorothiazide in a rapidly dissolving tablet.

Table 1 Estimated pharmacokinetic variables of hydrochlorothiazide (HCT) Mean values and s.e. mean ($n = 6$).

Dose	*AUC_{25}[a] (ng h ml^{-1})*	*t_{max} (h)*	*$C_{p\,max}$ (ng/ml)*	*$T_{\frac{1}{2}}$[b] (h)*
12.5 mg HCT	436 ± 62	1.9 ± 0.5	75 ± 17	2.4 ± 0.4
12.5 mg HCT + 100 mg metoprolol	468 ± 63	2.0 ± 0.4	74 ± 11	2.4 ± 0.2
25 mg HCT	1042 ± 167	1.3 ± 0.2	182 ± 31	2.5 ± 0.2
25 mg HCT + 100 mg metoprolol	834 ± 117	2.2 ± 0.3	136 ± 17	2.4 ± 0.3

a) Area under the plasma concentration *v.* time curve during 25 h after the administration.
b) Half-life between 2 and 8 h after the administration

Table 2 Urinary recovery of hydrochlorothiazide (HCT) during 48 h after administration of 12.5 and 25 mg HCT alone and in combination with 100 mg metoprolol.

	% of dose excreted in the urine			
Subject	*12.5 mg HCT*	*12.5 mg HCT 100 mg metroprolol*	*25 mg HCT*	*25 mg HCT 100 mg metoprolol*
JD	85.4	71.3	93.8	62.5
LB	51.8	46.2	66.3	46.6
US	43.0	74.8	96.2	85.2
ÅH	62.3	57.8	47.5	63.4
LW	73.8	70.7	93.4	91.2
TB	41.6	40.4	39.4	46.0
Mean	59.7	60.2	72.8	65.8
s.e. mean	7.1	5.9	10.3	7.7

The individual half-lives of metoprolol were virtually the same in both of the experiments and ranged between 2.5 to 7.5 h yielding a mean value of 4.4 ± 0.9 h. The area under the curve from zero to infinite time corrected for the dose, body weight and elimination half-life was 123 ± 6 mg/ml and 108 ± 20 mg/ml, respectively. For both of the combinations there was a fivefold interindividual variation in this area.

Discussion

The present study focuses on the biopharmaceutical and pharmacokinetic properties of metoprolol administered as a fixed combination product. For metoprolol alone these properties have been extensively studied in recent years (Regårdh, Borg, Johansson, Johnsson & Palmer, 1974; Johnsson, Regårdh & Sölvell, 1975; Regårdh, Johnsson, Jordö & Sölvell, 1975) and as regards HCT there are several reports on the bioavailability of various products (Tannenbaum, Rosen & Flanagan, 1968; McGilveray, Hossie & Matlock, 1973; Wagner, Gilleran & Zak, 1975; Beermann, Groschinsky-Grind & Lindström, 1977). Pharmacokinetic data of this drug were also recently reported by Beermann, Groschinsky-Grind & Rosén (1976).

Hydrochlorothiazide

In all four experiments with HCT the plasma levels declined bi-exponentially vs. time after the termination of the absorption phase. A similar time course of HCT has previously been reported by Beermann *et al.* (1976). These authors found an elimination half-life of the α-phase of 1.7 h and 13.1 h for the β-phase. Due to the experimental design it is not feasible to determine the elimination half-lives of these two phases with acceptable precision in the present study. However, between the second and eighth hour after the administration the plasma levels declined approximately monoexponentially. The half-life of the plasma concentration in this interval which should approximate $T_{\frac{1}{2}}\alpha$ was about 2.5 h for both of the HCT doses irrespectively of the drug being given alone or together with 100 mg metoprolol. The almost identical HCT plasma levels for both of the 12.5 mg doses 24 and 25 h after the administration (Figure 1) further indicate that also the half life of HCT in the beta-phase is unaffected by the β-adrenoceptor blocking agent. This was further confirmed in five of the subjects receiving the higher HCT dose. Due to inexplicably high plasma levels of HCT in one subject on the day after the administration of the solution, however, the average plasma levels of this dose were about three times higher at the end of the observation period than for the combination with metoprolol (Figure 2).

As metoprolol had no essential effect on the plasma levels of HCT the AUC_{25} values for the solution and for the combination tablet were identical (Table 2), indicating that metoprolol in the given dose does not affect the extent of bioavailability of HCT. The urinary recovery of HCT during 48 h further supports this finding (Table 2). On the average 60 to 73% of the dose administered was excreted during this period which is about the same as previously reported (Beermann *et al.*, 1976). However great inter- and intra-individual variations in the recovered amounts were observed. As the metabolism of the drug is negligible and the excretion of the drug is almost completed after 48 h (Beermann *et al.*, 1976) this would indicate that the drug is erratically absorbed from the gastro-intestinal tract as all subjects denied the loss of any urine specimens.

Even the rate of bioavailability of HCT appears to be essentially unaffected by the administration of metoprolol as shown by the t_{max} values in Table 1. The lower value of 25 mg solution in comparison with the combined metoprolol-HCT tablet might depend on the dissolution step involved in the absorption phase of the latter preparation.

Metoprolol

The almost identical mean metoprolol plasma concentration curves after administration of 100 mg of the drug in combination with 12.5 and 25 mg HCT (Figure 3) indicate that the diuretic agent has no significant influence on the pharmacokinetics of metoprolol. The average half-life, 4.4 ± 0.9 h, is about the same as previously observed for separate doses of metoprolol (Bengtsson *et al.*, 1975; Regårdh *et al.*, 1975). A further indication that HCT does not affect the pharmacokinetic of the biopharmaceutic properties of metoprolol is obtained by the very close values of the adjusted AUC in this study and those obtained previously for 100 mg metoprolol given to another group of six healthy subjects, three of whom also participated in the present experiment (Regårdh *et al.*, 1975).

Two of the subjects, however, had a longer plasma half-life of metoprolol (7.5 and 7.0 h, respectively) than hitherto observed. In a study by Regårdh *et al.* (1975) the corresponding half-lives in these two individuals were 6.1 and 5.5 h. The longer half-lives in the combination with HCT is probably due to individual variations rather than to an effect of the diuretic agent. This assumption is supported by the virtually identical half-lives of metoprolol in combination with both 12.5 and 25 mg HCT in these individuals and the fact that the half-life of metoprolol in the remaining four subjects was in the normal range when combined with HCT.

From the results obtained in this study it seems unlikely that some biopharmaceutic or pharmacokinetic interaction of therapeutic importance

would occur between metoprolol and HCT. This assumption, however, is based on results from a single dose study. A combination like the one tested, however, should normally be administered once daily which raises the question whether the results from the present study give relevant information. For metoprolol accumulation will be negligible due to the relatively short half-life of the drug. Therefore, single and repeated dosing will give about the same information. Consequently, metoprolol seems unlikely to affect the pharmacokinetics of HCT during long-term treatment.

With the once daily regimen HCT will accumulate in the plasma by about 40% assuming a half-life of 13 h (Beermann *et al.*, 1976). As a consequence of this the diurectic effect would be somewhat increased during steady state which might lead to a further decrease of the plasma volume. However, such a reduction is expected to have a very moderate influence on the plasma concentration and the effect of metoprolol due to its large volume of distribution.

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