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Lack of pharmacokinetic interaction between moxonidine and hydrochlorothiazide

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Moxonidine is an imidazoline-type antihypertensive agent, an agonist at central presynaptic α_2-adrenoceptors and imidazole receptors [1, 2]. It reduces the blood pressure in hypertensive patients and has few reported adverse effects [3]. Its systemic availability, pharmacokinetics after single and multiple dosing, and the effect of renal impairment on its disposition have been reported recently [4–7].

The concurrent administration of non-diuretic antihypertensives with hydrochlorothiazide is common, if the blood pressure cannot be well controlled by one drug alone.

Accordingly, the possible pharmacokinetic interaction of moxonidine with hydrochlorothiazide has been investigated. The study was approved by the local Ethics Committee and the Ethics Committee of the Bavarian Landesärztekammer.

The study, of open, randomized, crossover design, was done in 18 healthy male volunteers. Their mean (SD) age and weight were 35 (8) y and 72 (9) kg. All gave informed consent in writing to the study.

In the three study periods the subjects took moxonidine 0.2 mg b.d., hydrochlorothiazide 25 mg b.d., or the combination in randomised order. The drugs were given every 12 h for 6 days.

During accumulation (Days 1–5) blood samples were taken before each morning dose. On Day 6 blood samples were taken before dose and after the dose at 10, 20, 30, 45, 60, and 90 min, and 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 h. The 36 h blood sample was taken only for the determina-

Table 1. Pharmacokinetics (geometric means) of hydrochlorothiazide and moxonidine at steady-state after mono- and combination treatment ($n = 18$)

		Monotherapy	Combination treatment	Ratio (%)	(95% confidence interval)
Hydrochlorothiazide					
AUC_τ^{ss}	$[ng \cdot ml^{-1} \cdot h]$	935	967	103	(95–113)
$C_{predose}$	$[ng \cdot ml^{-1}]$	43	45	104	(92–116)
C_{max}	$[ng \cdot ml^{-1}]$	166	159	96	(85–109)
t_{max}[a]	[h]	2.2	2.1	97	(81–114)
$^2t_{1/2}$[b]	[h]	11.0	9.9	90	(73–112)
CL/f	$[ml \cdot min^{-1} \cdot kg^{-1}]$	6.2	6.0	97	(89–106)
$^2V_z/f$[b]	$[l \cdot kg^{-1}]$	5.7	5.0	87	(66–115)
Moxonidine					
AUC_τ^{ss}	$[pg \cdot ml^{-1} \cdot h]$	3176	3399	107	(96–119)
C_{max}	$[pg \cdot ml^{-1}]$	1225	1278	104	(89–122)
t_{max}[a]	[h]	0.70	0.62	88	(64–112)
$t_{1/2}$	[h]	1.8	1.9	107	(100–114)
CL/f	$[ml \cdot min^{-1} \cdot kg^{-1}]$	14.6	13.6	93	(84–104)
V_z/f	$[l \cdot kg^{-1}]$	2.3	2.3	100	(91–109)

[a] arithmetic evaluation; [b] $n = 17$

tion of hydrochlorothiazide. Plasma concentrations of moxonidine were determined by GC-MS (adapted from 5–7), and hydrochlorothiazide was measured by GC-ECD [8].

Throughout the study blood pressure and pulse rate were monitored before and 2 h after every dose and electrolyte status (sodium, potassium, calcium, chloride) was measured every second day.

The steady-state pharmacokinetics of moxonidine and hydrochlorothiazide were directly derived from the observed plasma levels after the last dose on Day 6 using standard methods.

After logarithmic transformation (except t_{max}), the pharmacokinetic data were subjected to analysis of variance using a general linear model [9, 10], and assessing sequence, period, and treatment effects, and subjects within sequence. Significance was defined as $P < 0.05$. 95 % confidence intervals for the geometric mean ratio between combination and monotherapy were calculated assuming monotherapy to be 100 % (arithmetic means for t_{max}).

The spectrum of adverse drug reactions that were noted, all of mild or moderate intensity, corresponded to the known pharmacodynamic profiles of hydrochlorothiazide and moxonidine. Only 3 subjects had a slight fall in potassium concentration.

Coadministration of moxonidine did not significantly alter the pharmacokinetics of hydrochlorothiazide (Table 1), nor did hydrochlorothiazide change the pharmacokinetics of moxonidine (Table 1).

In conclusion, the results of this multiple dose study of moxonidine and hydrochlorothiazide do not indicate any pharmacokinetic interaction.

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