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Pharmacokinetics of Atenolol and Metoprolol Administered together with Piroxicam

Hildegard Spahn[+], Peter Langguth[+], Dorit Krauss[+], Wilhelm Kirch[++] and Ernst Mutschler[+]

[+] Pharmakologisches Institut für Naturwissenschaftler, Theodor-Stern-Kai 7, Gebäude 75A, 6000 Frankfurt am Main 70
[++] Universitätsklinikum der Gesamthochschule Essen, Medizinische Klinik und Poliklinik, Hufelandstraße 55, 4300 Essen

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A possible pharmacokinetic interaction of atenolol or metoprolol and piroxicam was investigated over a period of 7 days. The mean plasma concentration versus time curve of atenolol (n=6) was nearly uninfluenced, whereas the mean metoprolol concentrations (n=6) were enhanced (statistically not significant). The pharmacokinetic parameters of both atenolol and metoprolol obtained from the plasma concentrations and urinary excretion on the 7. day of treatment were not significantly changed.

Pharmakokinetik von Atenolol and Metoprolol unter Piroxicam-Begleitmedikation

Die Pharmakokinetik von Atenolol und Metoprolol wurde unter gleichzeitiger Gabe von Piroxicam über einen Zeitraum von 7 Tagen untersucht. Bei Atenolol waren die mittleren Plasmaspiegel (n=6) gegenüber der Kontrollperiode kaum beeinflußt. Bei Metoprolol hingegen wurde eine Erhöhung der mittleren Konzentrationen gefunden, die aber nicht statistisch signifikant war. Die pharmakokinetischen Parameter von Atenolol und Metoprolol, die aus den Plasmakonzentrationen und der Urinausscheidung des 7. Tages der Untersuchung ermittelt wurden, waren nicht signifikant gegenüber der Kontrollperiode verändert.

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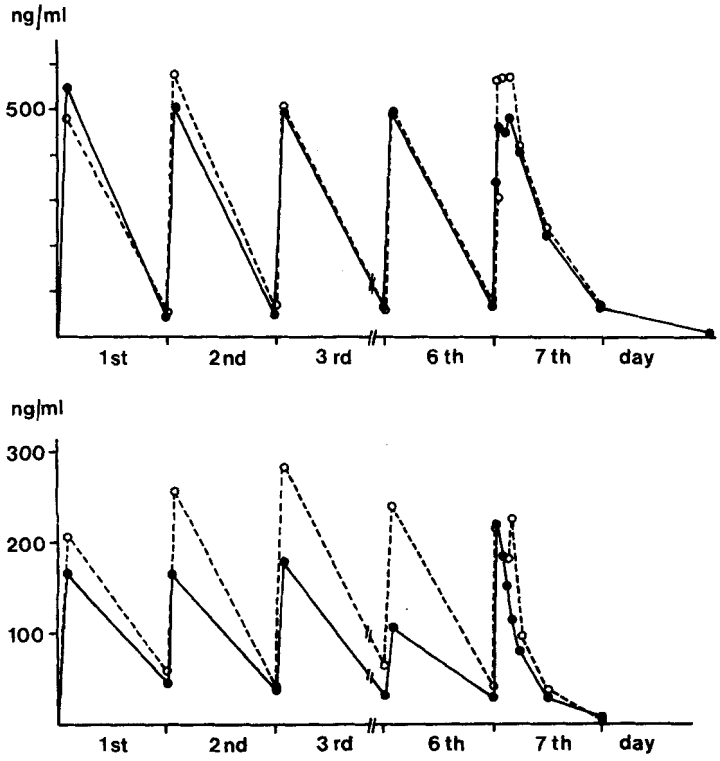
β-Receptor-antagonists interact with many drugs when given simultaneously. These interactions may either be due to pharmacokinetic or to pharmacodynamic mechanisms. Pharmacokinetic interactions may often result from changes in the oxidative drug metabolism[1),2),3)]. In this study a possible kinetic interaction of two β-receptor antagonists, the lipophilic and extensively metabolised metoprolol and the hydrophilic, non-metabolised atenolol, with piroxicam was investigated in healthy volunteers (n=6 for each β-antagonist, 7 days of treatment). Piroxicam is a widely used nonsteroidal antirheumatic drug.

With atenolol the mean concentrations are not influenced by the additional medication (fig. 1). This does not hold for metoprolol, where the means are higher, when the drug is administered together with piroxicam (fig. 2).

However, regarding the single volunteers, no uniform tendency can be observed, i. e. the concentrations are mostly higher, but also sometimes lower than in the control period. None of the pharmacokinetic parameters (tab. 1) of metoprolol obtained at day 7 is significantly changed by piroxicam. The C_{max}- and t_{max}- and the AUC-values are slightly higher than in the control period, whereas the terminal half-life is rather reduced.



Figures 1 and 2: Mean plasma concentrations of 6 healthy volunteers during 7 days of treatment with atenolol (Fig. 1) or metoprolol (Fig. 2) with and without piroxicam (straight line: control period; broken line: piroxicam period).

Table 1: Pharmacokinetic parameters ($\bar{x} \pm SD$) of atenolol (a) and metoprolol (b) in the control period and administered together with piroxicam

a) Atenolol	Control	Piroxicam
C_{max} (ng/ml)	679.2 ± 73	553.8 ± 138
t_{max} (h)	2.8 ± 0.8	3.4 ± 0.8
$t_{1/2}$ (h)	7.1 ± 3.3	7.0 ± 1.5
AUC ($ng \cdot ml^{-1} \cdot h$)	6594.0 ± 790	6204.2 ± 1780
CL_R (ml/min)	116.3 ± 24	96.9 ± 34
b) Metoprolol	**Control**	**Piroxicam**
C_{max} (ng/ml)	229.4 ± 158	334.0 ± 242
t_{max} (h)	1.2 ± 0.4	1.8 ± 1.2
$t_{1/2}$ (h)	4.6 ± 2.3	3.8 ± 1.2
AUC ($ng \cdot ml^{-1} \cdot h$)	1344.0 ± 1433	1652.5 ± 1690
CL_R (ml/min)	81.2 ± 40[1)]	79.3 ± 31[2)]

1) Urinary excretion data of only 3 volunteers were available (n = 3).
2) n = 5

In the case of atenolol the C_{max}-value and the mean amount that is excreted unchanged with the urine are lower (n. s.), if the drug is administered together with piroxicam, but there are no changes in any of the other kinetic parameters.

Piroxicam was detected in all analysed plasma samples except during the control period. From the individual plasma concentration time curves of the whole treatment period (fig. 3), it can be deduced that the piroxicam steady state concentrations were nearly reached on the day, when the pharmacokinetic parameters of the β-adrenoceptor antagonist were determined. This can be concluded, because the concentrations – in most cases – did no longer increase from day 6 to day 7.

Our investigations lead to the conclusion that there is no pharmacokinetic interaction between atenolol and piroxicam. As for metoprolol an increase in the mean concentrations could be observed, a kinetic interaction cannot be completely excluded, al-

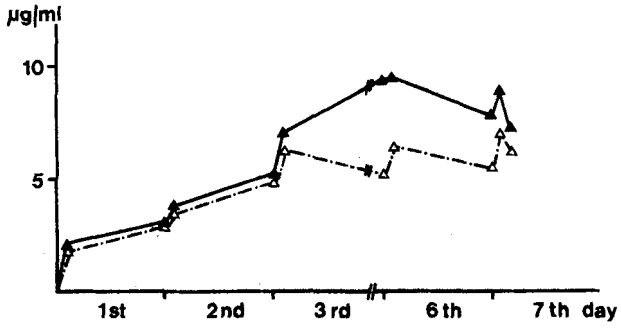


Figure 3: Mean piroxicam plasma concentrations (n=6) in the atenolol and the metoprolol group during 7 days of treatment (straight line: metoprolol; broken line: atenolol)

though the differences in the pharmacokinetic parameters are not statistically significant. Renal function does not seem to be influenced by piroxicam, as there were no changes in the atenolol half-lives, which are known to be correlated with changes of the GFR[4]. The still possible interaction of metoprolol and piroxicam is – at least from pharmacokinetic considerations – not so strong to give rise to clinical consequences. However, a pharmacodynamic interaction remains to be investigated for both compounds in hypertensive patients, as the antihypertensive effect of β-receptor antagonists might be reduced by nonsteroidal antiinflammatory drugs[5, 6], an interaction which is probably common to all of the β-adrenoceptor antagonists, but does not occur with all of the nonsteroidal antiinflammatory drugs[7].

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Experimental Part

Subjects and procedure: 12 young healthy volunteers (20–35 years, nonsmokers) took part in the investigation. An intraindividual comparison was performed. 6 of the volunteers were administered 100 mg of atenolol (Tenormin^R) once daily over a period of 7 days. The remaining 6 volunteers received metoprolol 100 mg (Lopresor^R) twice daily over 7 days. After a therapy-free interval of 2 days, 20 mg of piroxicam (Felden^R), were given twice daily together with the β-antagonist for 7 days. After the morning dose on day 7 the elimination kinetics of the β-receptor antagonists were studied.
Blood sampling times: on the 1st, 2nd, 3rd and 6th day of each of the treatment periods: before and 2 hours after the morning dose, on the 7th and 8th day: before, 1, 2, 3, 4, 6, 12, 24, and 48 hours after the last administration (day 7).
Blood (heparin-treated) was centrifuged immediately, and the plasma was stored frozen (–20 °C) until analysis. Urine was collected up to 24 hours after the morning dose on day 7.

Assay methods

Reference compounds: atenolol (ICI Pharmaceuticals, Plankstadt), metoprolol tartrate (Astra Chemicals, Wedel/Holstein), piroxicam pure substance and metabolites (Pfizer, Karlsruhe).
Chemicals and instruments: solvents and TLC plates (E. Merck, Darmstadt), EDTN (1-ethoxy-4-(2.4-dichloro-1.3.5-triazinyl)naphthalene) (BDH Chemicals Ltd., Poole, England); Linomat III (Camag, Muttenz, Switzerland), chromatogram spectrophotometer KM 3 (Zeiss, Oberkochen).

Quantitative determinations in plasma and urine samples:

Atenolol and metopolol were determined by quantitative thin-layer chromatography (TLC)[8, 9]. Modification for metoprolol: A solution of EDTN in ethylacetate was added to the residue. 20 ml of this solution were applied on TLC plates (20 × 20 cm, silica gel 60, without fluorescent indicator, 5 mm-strip). The chromatograms were developed (20 cm) twice with chloroform LiChrosolv^R, ethyl acetate, cyclohexane (92:3:5, v/v, saturated atmosphere). Urine samples (0.2 ml + 0.8 ml H_2O) were treated as plasma samples. Piroxicam and its major metabolites do not interfere neither with the atenolol nor with the metoprolol assay.

Piroxicam resorption (and accumulation in plasma) was tested by measuring the drug concentration in plasma on days 1, 2, 3, 6, and 7 before and 2 h after the morning dose in each of the treatment periods (on day 7 additionally after 4 h): The HPTLC method of Riedel[10] was used in a slightly modified form. Atenolol and metoprolol did not interfere with the piroxicam assay.

Pharmacokinetic and statistical analyses: The calculation of the pharmacokinetic parameters included the values from 8 a. m. of the 7th until 8 a. m. of the 8th day. Maximal plasma concentrations observed (C_{max}) and the according time values (t_{max}), terminal half-lives ($t_{1/2}$), areas under the plasma concentration time curves of the 7th day (AUC_7), cumulative urinary excretion of the drugs on day 7 (Ae_7), and the renal clearance (CL_R) were determined. Terminal half-lives were estimated by linear regression analysis (slope $= \lambda_z$). Rate constants and half-lives were also determined using the ADAPT program[11] on a DEC 10. AUC_7 values were calculated by the trapezoidal method. CL_R is the quotient of Ae_7 and AUC_7. Values are expressed as mean ($\bar{x}$) and standard deviation (SD). The Student's t-test[12] was used for the statistical analyses ($p > 0.05$ = n. s.).

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