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# INFLUENCE OF INFLAMMATORY DISEASE ON THE CLINICAL PHARMACOKINETICS OF ATENOLOL AND METOPROLOL*

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## ABSTRACT

The influence of inflammatory disease on the pharmacokinetics of atenolol and metoprolol was investigated after administering single oral 100 mg doses of the drugs to six subjects. Each subject had a respiratory tract infection with an erythrocyte sedimentation rate (ESR) of over 20 mm in the first hour and a body temperature of at least 38·5 °. Since the subjects subsequently received atenolol and metoprolol when they were healthy, each person acted as his own control.

Inflammatory disease had no influence on the kinetics of metoprolol. In contrast, mean peak plasma levels and AUC for atenolol were significantly lower, both by about 40 per cent, during infectious disease compared to the healthy state ($p < 0{\cdot}05$), where as renal clearance of atenolol slightly increased from $110{\cdot}8 \pm 14{\cdot}7$ ml min$^{-1}$ in the healthy state to $128 \pm 21{\cdot}6$ ml min$^{-1}$, when the ESR's were elevated. The elimination half-life of atenolol, about 10 h, was not affected by the health status of the subjects. Reduced absorption in the gastro-intestinal tract and enhanced elimination of atenolol from plasma might account for the decreased AUC and peak plasma levels of the drug during inflammatory disease.

KEY WORDS Inflammatory disease Clinical pharmacokinetics Atenolol Metoprolol

## INTRODUCTION

Several circumstances may alter the normal pharmacokinetics of atenolol, e.g. kidney disease [1–4] or concurrently administration of certain drugs.[5, 6] Since atenolol is almost entirely excreted via the kidneys,[7] accumulation of the drug could have been expected primarily in patients with renal insufficiency. A

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hydrophilic betareceptor blocker like atenolol is only absorbed from the intestine to about 50 per cent, since such substances do not cross cellular membranes readily.[8] Thus it seems to be possible that concomitantly applied drugs would inhibit the absorption of atenolol to a greater extent. This has been confirmed by concurrent administration of atenolol with calcium, ampicillin or aluminium hydroxide.[5,6] Cimetidine did not influence atenolol kinetics, despite the fact that in the case of metoprolol or propranolol an impressive interaction with cimetidine has been described.[9-12] Inflammatory disease is known to increase levels of beta blockers such as oxprenolol or propranolol, although those of metoprolol were not altered.[13-15] The mean plasma propranolol concentrations were also higher than in normal controls in patients with celiac disease. Those of practolol in the celiacs, however, lagged behind those of the normal subjects.[16] The aim of the present study was to investigate the influence of inflammatory disease of the respiratory tract on the kinetics of atenolol and of metoprolol. Each patient studied was treated during infectious disease and later on in the healthy state, so that each acted as his own control.

## PATIENTS AND METHODS

Six patients with inflammatory disease of the respiratory tract were investigated (mean age $28{\cdot}8 \pm 2{\cdot}6$ years; range 20 to 37 years; 2 male, 4 female; mean body weight $62{\cdot}2 \pm 4{\cdot}1$ kg). They had given their informed consent to participate in the study. When the treatment with beta blockers was started, all patients had an erythrocyte sedimentation rate (ESR) of over 20 mm in the first hour (mean ESR $39 \pm 7{\cdot}9$ mm; range 23 to 68 mm in those receiving atenolol; mean ESR $33{\cdot}5 \pm 2{\cdot}5$ mm; range 29 to 43 mm in those receiving metoprolol) and body temperature of all of them was over 38·5° (mean $39{\cdot}2 \pm 0{\cdot}3°$ in those receiving atenolol; mean $38{\cdot}9 \pm 0{\cdot}1°$ in those receiving metoprolol). All had symptoms of a respiratory tract infection such as rhinitis, cough, hoarseness, sore throat, and palpable regional lymph nodes. The patients had no signs of kidney and liver dysfunction nor did the hematological and biochemical screening yield abnormal results. Concomitant medication had been withdrawn 2 days prior to

Table 1. Summary of abbreviations, definitions and equations

| Abbreviation | Meaning |
|---|---|
| $K_{el}$ | Elimination rate constant |
| $C_{max}$ | Maximum plasma concentration |
| $T_{max}$ | Time to reach $C_{max}$ |
| $T_{\frac{1}{2}}$ | Half-life of elimination |
| $AUC_{0\to\infty}$ | Area under the plasma level–time curve calculated by the trapezoidal rule and extrapolated to infinity |
| $Cl_r$ | Renal clearance = $A_u\infty/AUC_{0\to\infty}$ |
| $A_u\infty$ | Cumulative urinary excretion up to $\infty$ |

Table 2. Pharmacokinetic parameters of the six subjects (with $\bar{X} \pm$ S.E.M.) during inflammatory disease and in the healthy state following ingestion of atenolol 100 mg

| | Subject No. | $C_{max}$ (ng ml$^{-1}$) | $T_{max}$ (h) | $AUC_{0\to\infty}$ (ng ml$^{-1}$ h) | $K_{el}$ (h$^{-1}$) | $T_{\frac{1}{2}}\beta$ (h) | $A_u\infty$ (mg) | $Cl_r$ (ml min$^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| Inflammatory disease | 1 | 243 | 4 | 3066·4 | 0·0619 | 11·2 | 36·1 | 196·2 |
| | 2 | 399 | 3 | 3658·9 | 0·0673 | 10·3 | 18·8 | 85·6 |
| | 3 | 449 | 4 | 4794·9 | 0·0779 | 8·9 | 37·3 | 129·7 |
| | 4 | 341 | 3 | 5616·8 | 0·0481 | 14·4 | 26·7 | 79·2 |
| | 5 | 317 | 1 | 3417·9 | 0·0990 | 7·0 | — | — |
| | 6 | 513 | 3 | 5209·9 | 0·0797 | 8·7 | 46·7 | 149·4 |
| | $\bar{X}$ | 377·0 | 3·0 | 4294·1 | 0·0723 | 10·1 | 33·1* | 128·0* |
| | ±S.E.M. | 39·6 | 0·4 | 428·9 | 0·0071 | 1·0 | 4·8 | 21·6 |
| Healthy state | 1 | 456 | 3 | 4643·3 | 0·0686 | 10·1 | 43·1 | 154·7 |
| | 2 | 653 | 2 | 6712·3 | 0·0636 | 10·9 | 37·0 | 91·9 |
| | 3 | 708 | 2 | 7028·0 | 0·0788 | 8·8 | 29·8 | 70·7 |
| | 4 | 1049 | 2 | 16 760·3 | 0·0485 | 14·3 | 42·2 | 42·0 |
| | 5 | 428 | 2 | 5558·4 | 0·0912 | 7·6 | — | — |
| | 6 | 550 | 1 | 4436·2 | 0·0722 | 9·6 | 28·9 | 108·6 |
| | $\bar{X}$ | 640·7 | 2·0 | 7523·1 | 0·0704 | 10·2 | 36·2* | 110·8* |
| | ±S.E.M. | 92·9 | 0·3 | 1896·6 | 0·0058 | 0·9 | 3·0 | 14·7 |

*$n = 5$.

and during the course of the study. Four to 8 weeks later when the ESR and body temperature were normal and the subjects felt well, atenolol as well as metoprolol were again applied in the same way as during inflammatory disease. Thus each person acted as his own control in a simple crossover design.

One tablet of atenolol 100 mg or metoprolol 100 mg were administered as single dose to each subject at 7.00 a.m. with 100 ml water and after an overnight fast. Standardized drinks and meals were given throughout the study at noon, in the evening and in the morning at 8.00 a.m. Blood samples were withdrawn before application, 0·5, 1, 2, 3, 4, 6, 12, 24, 36, and 48 h afterwards. Urine was collected from 0–4, 4–8, 8–12, 12–24, and 24–48 h. Because of difficulties with urine collection not all of the urine samples could be included in the statistical evaluation (see Table 2 and 3). Atenolol (Tenormin®) and metoprolol (Lorpresor®) were administered as conventional commercial preparations. Blood was centrifuged immediately after being withdrawn. Plasma and urine samples were stored frozen (−20°) until determination of atenolol and metoprolol concentrations.

Atenolol was determined in plasma and urine samples according to a modification of the fluorodensitometric method recently described by us.[17] 0·5 ml 1*N* NaOH and 0·5 g NaCl were added to 1 ml plasma or urine. The mixture was shaken with 0·4 ml cyclo-hexane–butanol (1 : 1). After centrifuging, 10 to 80 µl of the organic layer were spotted on to a thin-layer plate. Development and scanning of the plate were performed as described previously.[17] Metoprolol was also estimated by a fluorimetric method[18] using oxprenolol as internal standard. Atenolol could be quantitated in plasma up to a concentration of 5 ng ml$^{-1}$, in urine up to 50 ng ml$^{-1}$. Detection limit of metoprolol in plasma was 1 ng ml and in urine 20 ng ml$^{-1}$.

Pharmacokinetic parameters of each patient were calculated as defined in Table 1. Statistical evaluation included the Wilcoxon test.[19] Values are expressed as mean ($\bar{X}$) and standard error of the mean (S.E.M.).

## RESULTS

### *Pharmacokinetics of atenolol in inflammatory disease*

Figure 1 shows the mean plasma atenolol concentration–time curves of the subjects with elevated ESR and with normal ESR. In Table 2 mean pharmacokinetic parameters of the subjects during inflammatory disease and in the healthy state are described. The time to reach peak plasma levels ($T_{max}$) did not differ significantly between the healthy state and infectious disease, whereas mean peak plasma concentrations were significantly lowered with 344·0 ± 39·6 ng ml during disease state compared to 640·7 ± 92·9 ng ml$^{-1}$ in the healthy state ($p < 0·05$). The difference in plasma atenolol concentrations at each sampling time from 1 to 6 h after dosing between subjects with high ESR and in the control state with normal ESR was significant with $p < 0·05$. Correspond-

Table 3. Pharmacokinetic parameters of the six subjects (with $\bar{X} \pm$S.E.M.) during inflammatory disease and in the healthy state following ingestion of metoprolol 100 mg

| | Subject No. | $C_{max}$ (ng ml$^{-1}$) | $T_{max}$ (h) | $AUC_{0\rightarrow\infty}$ (ng ml$^{-1}$ h) | $K_{el}$ (h$^{-1}$) | $T_{\frac{1}{2}}\beta$ (h) | $A_u\infty$ (μg) | $Cl_r$ (ml min$^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| Inflammatory disease | 1 | 233 | 3 | 2970·9 | 0·0592 | 11·7 | 12 118 | 68·0 |
| | 2 | 356 | 2 | 1784·2 | 0·1691 | 4·1 | — | — |
| | 3 | 46 | 2 | 95·2 | 0·5776 | 1·2 | 1961 | 18·3 |
| | 4 | 184 | 4 | 1419·2 | 0·1308 | 5·3 | 7661 | 90·0 |
| | 5 | 143 | 3 | 486·4 | 0·1540 | 4·5 | — | — |
| | 6 | 27 | 1 | 94·9 | 0·2166 | 3·2 | 824 | 144·7 |
| | $\bar{X}$ | 164·8 | 2·5 | 1141·8 | 0·2178 | 5·0 | 5641·0* | 80·2* |
| | ±S.E.M. | 50·1 | 0·4 | 463·9 | 0·0749 | 1·5 | 2626·4 | 26·2 |
| Healthy state | 1 | 160 | 3 | 2165·7 | 0·0976 | 7·1 | 8119 | 62·5 |
| | 2 | 284 | 2 | 2361·8 | 0·1733 | 4·0 | — | — |
| | 3 | 213 | 1 | 747·2 | 0·3014 | 2·3 | 2637 | 58·8 |
| | 4 | 30 | 6 | 228·4 | 0·2166 | 3·2 | 689 | 50·3 |
| | 5 | 81 | 2 | 645·1 | 0·1691 | 4·1 | — | — |
| | 6 | 35 | 1 | 185·5 | 0·2310 | 3·0 | 997 | 89·6 |
| | $\bar{X}$ | 133·8 | 2·5 | 1055·6 | 0·1981 | 3·9 | 3110·5* | 65·3* |
| | ±S.E.M. | 41·9 | 0·8 | 393·4 | 0·0280 | 0·7 | 1723·4 | 8·5 |

* $n = 4$.

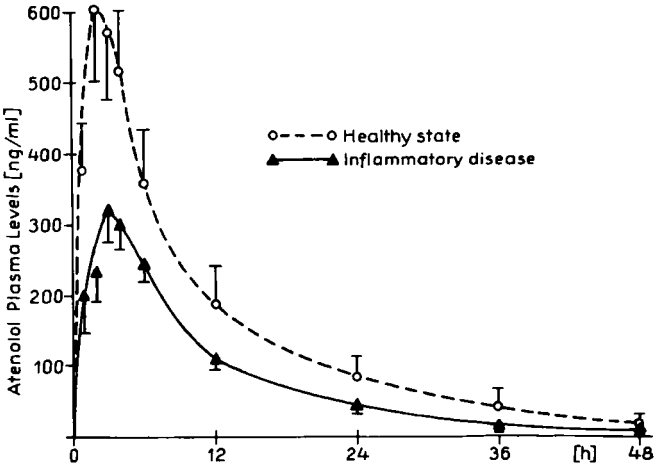


Figure 1. Mean atenolol plasma concentrations ($\bar{X} \pm$S.E.M.) of six subjects with inflammatory disease (ESR > 20 mm in the first hour) and in the healthy state

ingly the areas under the plasma concentration–time curve (AUC) were $4294{\cdot}1 \pm 428{\cdot}9$ ng ml$^{-1}$ h during infection and $7523{\cdot}1 \pm 1896{\cdot}6$ ng ml$^{-1}$ h in the healthy state ($p < 0{\cdot}05$). Renal clearance of atenolol rose to $128{\cdot}0 \pm 21{\cdot}6$ ml min$^{-1}$ when ESR was high compared to $110{\cdot}8 \pm 46{\cdot}4$ ml min$^{-1}$ when ESR was in the normal range ($p < 0{\cdot}05$). There were significant correlations between the height of the ESR on one hand and AUC values ($p < 0{\cdot}01$) as well as mean peak atenolol concentrations ($p < 0{\cdot}01$) on the other hand.

Elimination rate constant and elimination half-life of atenolol were about the same in elevated ESR and normal ESR; the half-life amounted to nearly 10 h. In

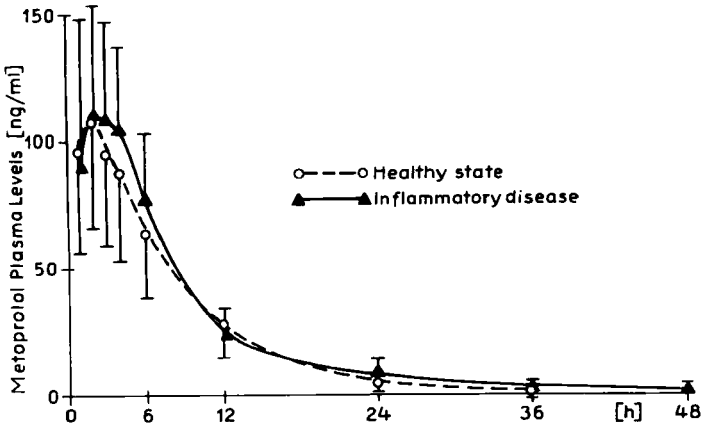


Figure 2. Mean metoprolol plasma concentrations ($\bar{X} \pm$S.E.M.) of six subjects with inflammatory disease (ESR > 20 mm in the first hour) and in the healthy state

one subject the reproducibility of the plasma concentration–time curve in the healthy state has been confirmed three times.

*Pharmacokinetics of metoprolol in inflammatory disease*

Figure 2 shows the mean plasma metoprolol concentration–time curve of the subjects during inflammatory disease and in good health. In Table 3, mean kinetic parameters of the subjects in both states are described. There were no significant differences in any of the average kinetic data between healthy subjects and patients with infectious disease. When the ESR was raised the mean AUC amounted to $1141{\cdot}8 \pm 453{\cdot}9\,\mathrm{ng\,ml^{-1}\,h}$ compared to $1055{\cdot}6 \pm 393{\cdot}4\,\mathrm{ng\,ml^{-1}\,h}$ in the normal state ($p > 0{\cdot}05$). There were no obvious correlations between the height of the ESR and the mean peak plasma levels or the AUC of metoprolol.

## DISCUSSION

In 1979 Schneider *et al.*[13] found that patients in the active stage of various inflammatory disease attain much higher plasma propranolol concentrations than healthy controls. Kendall *et al.*[14] in the same year reported similar, though considerably less pronounced results with oxprenolol. Plasma metoprolol concentrations of patients with high ESR (over 20 mm after the first hour) could not be shown to differ significantly from those of healthy volunteers and also the AUC's of both groups were almost identical.[15] In these three studies the underlying disease which caused a raised ESR were mostly rheumatoid arthritis, Crohn's disease, ulcerative colitis, and only few other illnesses. Although only patients with a respiratory tract infection as reason for elevated ESR were included in the present study, our results with metoprolol are very similar to those of Schneider *et al.*[15] They confirm that plasma metoprolol levels, AUC and other kinetic parameters of the drug are not altered by inflammatory disease. Furthermore, comparing this with the other reported studies, it should be noted that in our study the subjects acted as their own controls; thus after recovering from inflammatory disease, the kinetic study was repeated with them in the healthy state.

Propranolol, oxprenolol, and metoprolol are all predominantly metabolized by the liver, but they differ in the extent of their binding to plasma proteins: 93 per cent of propranolol is bound, 80 per cent of oxprenolol and only 11 per cent of metoprolol.[20] Thus increased binding to acute phase reactant proteins, which rise in inflammatory disease, might be a possible explanation for the high plasma levels of propranolol and oxprenolol in patients with elevated ESR. Therefore metoprolol, which has a lower affinity to plasma proteins, does not appear to accumulate in infectious disease. The increased protein-binding of drugs such as propranolol or oxprenolol could lead to raised plasma concentrations of these drugs. The mode of action might be due to reducing the

apparent volume of distribution or possibly due to a protection from metabolism during the first pass through the liver. Completely different from the facts mentioned so far are the results for atenolol kinetics in inflammatory disease. Plasma levels and AUC of atenolol are significantly reduced in subjects with high ESR compared to those with normal ESR, whereas renal clearance of the drug is increased. In contrast to lipophilic substances like propranolol, oxprenolol or metoprolol, atenolol is a more hydrophilic drug; it is only 3 per cent protein bound.[21] Hydrophilic beta blockers tend not to be metabolized extensively and do not cross cellular membranes readily.[8] Thus atenolol is only about 50 per cent absorbed from the gastro-intestinal tract following oral ingestion.[1-4] As an interpretation of our results with atenolol, it seems to be possible that inflammatory disease leads to a further reduction in the degree of absorption of atenolol from the gastro-intestinal tract. This remains plausible even though we found no significant difference between the urinary recovery of atenolol from the healthy subjects and those with infectious disease. Incomplete urine collection can not be ruled out as a reason for this apparent inconsistency between relative extents of absorption as measured from the urinary and blood level data. It is concluded that subjects who are treated with atenolol during inflammatory disease should be monitored carefully for the desired effect of the beta blocker especially 6 and 12 h after dosing; it may be necessary to increase the atenolol dosage. Another consideration may be therapeutically important for patients with an acute respiratory tract infection who are treated simultaneously with ampicillin; this drug lowers atenolol plasma levels by about 50 per cent[22]; both disease state and drug interaction effects may then be additive and lead to very low plasma atenolol concentrations.

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## REFERENCES

1. J. Sassard, N. Pozet, J. McAinsh, J. Legheand and P. Zech, *Eur. J. Clin. Pharmacol.*, **12**, 175 (1977).
2. S. H. Wan, R. Z. Koda and R. F. Maronde, *Br. J. Clin. Pharmacol.*, **7**, 569 (1979).
3. J. McAinsh, B. F. Holmes, S. Smith, D. Hood and B. Warren, *Clin. Pharmacol. Ther.*, **28**, 302 (1980).
4. W. Kirch, H. Köhler, E. Mutschler and M. Schäfer, *Eur. J. Clin. Pharmacol.*, **19**, 65 (1981).
5. C. G. Regardh, P. Lundborg and B. A. Persson, *Biopharm. drug. dispos.*, **2**, 79 (1981).
6. W. Kirch, M. Schäfer-Korting, T. Axthelm, H. Köhler and E. Mutschler, *Clin. Pharmacol. Ther.*, **30**, 429 (1981).
7. P. R. Reeves, J. McAinsh, D. A. D. McIntosh and M. J. Winrow, *Xenobiotica*, **8**, 313 (1978).
8. J. M. Cruickshank, *Am. Heart J.*, **100**, 160 (1980).
9. J. Feely, G. R. Wilkinson and A. R. Wood, *New Engl. J. Med.*, **304**, 692 (1981).
10. J. W. Reimann and J. C. Frohlich, *Naunyn–Schmiedeberg's Arch. Pharmacol.*, **316** (Suppl.), 1279 Abstr. 315 (1981).

11. A. M. Heagerty, M. A. Donovan, C. M. Castleden, J. I. Pohl, L. Patel and A. Hedges, *Br. Med. J.*, **282**, 1917 (1981).
12. W. Kirch, H. Köhler, H. Spahn and E. Mutschler, *Lancet*, **ii**, 531 (1981).
13. R. E. Schneider, H. Bishop and C. F. Hawkins, *Br. J. Clin. Pharmacol.*, **8**, 43 (1979).
14. M. J. Kendall, C. P. Quaterman, H. Bishop and R. E. Schneider, *Br. Med. J.*, **2**, 465 (1979).
15. R. E. Schneider, H. Bishop, M. J. Kendall and C. P. Quaterman, *J. Clin. Pharmacol. Ther. Toxicol.* **19**, 158 (1981).
16. R. L. Parsons, C. M. Kaye, K. Raymond, J. R. Traunce and P. Turner, *GUT*, **17**, 139 (1976).
17. M. Schäfer and E. Mutschler, *J. Chromatogr.*, **169**, 477 (1979).
18. M. Schäfer and E. Mutschler, *J. Chromatogr.*, **64**, 247 (1979).
19. L. Sachs, *Angewandte Statistik*, Springer-Verlag, Berlin, Heidelberg, New York 5. 1978. neubearb. Aufl., S. 242.
20. W. Diess, S. Brechthütter and W. Theobald, *Aust. N. Z. J. Med.*, **6**, 365 (1976).
21. H. E. Barber, H. M. Hawksworth, N. R. Kitterington, J. Petersen, J. C. Petrie and J. M. Sevann, *Br. J. Clin. Pharmacol.*, **6**, 446 (1977).
22. M. Schäfer-Korting, W. Kirch, T. Axthelm, H. Köhler and E. Mutschler, *Clin. Pharmacol. Ther.*, accepted for publication (1982).