Drug interaction between propafenone and metoprolol

F. WAGNER, D. KALUSCHE, D. TRENK, E. JÄHNCHEN & H. ROSKAMM
Rehabilitationszentrum, Bad Krozingen, FRG

1 The steady-state plasma concentrations of metoprolol and propafenone were determined in patients being treated with one of these drugs alone and during combined treatment with both drugs. In addition, single dose studies with metoprolol, propafenone and the combination of both drugs were performed in healthy volunteers to determine the pharmacokinetics and the time course of β -adrenoceptor blocking activity.

2 In four patients being treated with metoprolol first and subsequently with propafenone in addition steady-state levels of metoprolol increased two to five fold with simultaneous treatment with propafenone.

3 In four patients being treated with the drug combination first and thereafter with propafenone alone no changes in the steady-state levels of propafenone were observed between both treatment periods.

4 Adverse effects of the drug combination were observed in two patients (one patient experienced severe nightmares and the other left ventricular failure).

5 When single oral doses of metoprolol (50 mg) and propafenone (150 mg) and the combination of both were administered to healthy subjects, an approximately two-fold decrease of the oral clearance of metoprolol was seen when propafenone was given in addition. No conclusive changes in the pharmacokinetics of propafenone could be detected in the presence of metoprolol.

6 Duration of β -adrenoceptor blocking activity of a single dose of metoprolol in healthy volunteers as measured by reduction of exercise-induced tachycardia increased when propafenone was given in addition.

7 The dose of metoprolol should be reduced when propafenone is given in addition.

Keywords propafenone metoprolol drug interaction

Introduction

Patients suffering from coronary heart disease and ventricular arrhythmias often receive β -adrenoceptor antagonists in combination with class I antiarrhythmic drugs.

Also for the treatment of ventricular arrhythmias itself such a combination is thought to be favourable in order to enhance the antiarrhythmic effect and to reduce the side effects of antiarrhythmic drugs (Lüderitz, 1986). Such a

drug combination may consist of metoprolol and the class I antiarrhythmic drug propafenone. Investigations on possible drug interactions between both compounds are lacking. Such interactions are likely since both drugs are eliminated by biotransformation and undergo a marked first-pass extraction by the liver (Regårdh & Johnson, 1980; Hollman *et al.*, 1983; Connolly *et al.*, 1983; Siddoway *et al.*, 1984). Thus, we in-

vestigated the effect of propafenone on the kinetics of metoprolol and *vice versa* in patients who had been treated with these drugs and also in healthy volunteers.

Methods

Two studies were carried out: study A in eight patients treated for cardiovascular disease and study B in six healthy male volunteers.

Study A in patients

Eight patients who were all treated for ventricular arrhythmias (Lown classification IV a and b) were included in the study. Patients details are shown in Table 1. Patients received commercially available metoprolol tartrate tablets (50 and 100 mg—Lopresor®) and propafenone-HCl tablets (150 mg—Rytmonorm®).

Four of the eight patients (patients 1–4) were treated with metoprolol for 1–4 weeks (either 50 mg three times daily or 100 mg twice daily) prior to the study and were considered to have steady-state plasma levels of metoprolol. On the first study day 6 blood samples of 10 ml were

obtained at 0, 1, 2, 3, 4 and 6 h during a dosing interval. The patients were then placed on concomitant propafenone therapy (150 mg three times daily). Four days later again six blood samples were drawn at 0, 1, 2, 3, 4 and 6 h during a dosing interval. At this time the propafenone concentrations were considered to have reached steady-state since Conolly *et al.* (1983) reported half-lives of propafenone between 2.4 and 11.8 h following chronic oral therapy.

Four other patients (patients 5–8) were treated with metoprolol (50 mg three times daily) and propafenone (150 mg three times daily) for 1 week (patients 6–8) and 6 months (patient 5) prior to the study. On the first study day six blood samples of 10 ml were obtained at 0, 1, 2, 3, 4 and 6 h during a dosing interval. The metoprolol therapy was subsequently discontinued and 4 days later again six blood samples were obtained at 0, 1, 2, 3, 4 and 6 h during a dosing interval. In both studies samples were obtained during the same dosing interval of the day.

All blood samples were obtained from a cubital vein via an indwelling catheter. The samples were collected in heparinised syringes, centrifuged for 5 min at 4000 rev min⁻¹ and the plasma stored frozen at -20° C until assayed.

Table 1 Patients details

Patient	Age (years)	Sex	Diagnosis and clinical status	Concomitant therapy
1	40	M	CAD MI BS	Phenprocoumon, digitalis
2	57	M	CAD MI	ASA
3	51	M	CAD MI BS	Phenprocoumon
4	67	F	AS AVR	ASA Lactulose
5	43	M	CAD MI	Nifedipine ASA, hydrochlorothiazide, amiloride
6	56	M	CAD MI	Nifedipine, ISDN
7	58	M	CAD	Nifedipine, ISDN
8	50	M	CAD MI BS	Phenprocoumon ISDN

CAD: coronary artery disease; BS: by-pass surgery; AS: aortic stenosis; MI: myocardial infarction; AVR: aortic valve replacement; ISDN: Isosorbide dinitrate; ASA: acetylsalicylic acid.

Study B in healthy volunteers

Six healthy male volunteers (age 27.5 ± 3.5 years, height 181.3 ± 4.4 cm and bodyweight 74.3 ± 8.4 kg, mean $\pm$ s.d.) participated. The study was approved by the local ethics committee and all volunteers gave their written consent. All subjects were athletic individuals and prior to the study all of them underwent a 24 h Holter-monitoring and a maximal exercise test until exhaustion in supine position on a bicycle ergometer.

All volunteers received in a three-way open randomised crossover study using a latin-square design 50 mg metoprolol tartrate, 150 mg propafenone HCl and a combination of 50 mg metoprolol tartrate and 150 mg propafenone HCl 1 week apart. On the day when the combination of both drugs was administered, 150 mg propafenone were given 30 min prior to the administration of 50 mg metoprolol.

After an overnight fast a light breakfast was given at 07.00 h, and 90 min later an exercise ECG was performed. Thereafter a blood sample was obtained, and the volunteers ingested the medication. Additional exercise tests were performed after 1.5, 3, 6, 8 and 12 h and blood samples were drawn at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h following administration of metoprolol.

Blood samples were centrifuged and the plasma stored at -20°C until assayed.

All subjects were familiarised with the exercise protocol before the study and had been exposed to blood sampling techniques. Consumption of alcohol, caffeine and nicotine was not permitted. The studies were performed at the same time of the day for each study period.

Drug analysis

Metoprolol was measured by high performance liquid chromatography using the method described by Briant *et al.* (1983). Propafenone was determined by high performance liquid chromatography according to the procedure published by Brode *et al.* (1982). Specificity of the applied assays was checked by co-analysis of plasma samples derived from patients treated with either metoprolol or propafenone alone. The lower limit of quantification (coefficient of variation of calibration standards less than 10%) for both compounds was approximately 10 ng ml^{-1} .

Exercise protocol

Exercise-tests were performed on an electrically-braked ergometer in supine position. The test was started at 50 watts and work-load was in-

creased stepwise by 50 watts every 2 min up to 200 watts. Blood pressure was measured every 2 min and heart-rate was taken as the mean of 10 consecutive R-R intervals of the ECG recordings at the end of each exercise-step. β -adrenoceptor blocking effect was evaluated as reduction of exercise induced tachycardia at the highest work load (200 watts, except one subject who could only exercise up to 150 watts) compared to a drug-free exercise test performed before the intake of drugs.

Pharmacokinetic analysis

Plasma concentration-time data at steady-state obtained in patients was fitted according to a one-compartment model with first order absorption using the TOPFIT-program (Thomae, Biberach, FRG). The plasma concentration-time curves in healthy volunteers following administration of a single oral dose of propafenone or metoprolol could more adequately be described by two compartment characteristics. The average steady-state concentration ($C_{ss,av}$) and the oral clearance (CL/F) were calculated as:

$$C_{ss,av} = \frac{AUC_{\tau}}{\tau}$$

$$\text{and } CL/F = \frac{\text{Dose}/\tau}{AUC_{\tau}}$$

Following single oral doses the oral clearance (CL/F) was calculated:

$$CL/F = \frac{\text{Dose}}{AUC_{0-\infty}}$$

where AUC_{τ} is the integral of the plasma concentration time course within the desired dosing interval τ , $AUC_{0-\infty}$ the total area extrapolated to infinity and F the bioavailability.

Statistical analysis

The AUCs in patients without and with administration of the second drug and also the pharmacokinetic parameters obtained in healthy volunteers were compared by paired *t*-test. Analysis of variance for repeated measurements was used to test for differences in the time courses

of the β -adrenoceptor blocking effect. Statistical significance was set at 5%.

Results

Study A in patients

Figure 1 shows the plasma concentrations of metoprolol during a dosing interval when the four patients received metoprolol alone and under concomitant treatment with propafenone. In all four patients metoprolol concentrations increased several-fold when propafenone was added. The average steady-state concentrations of metoprolol tartrate were 49.0, 125.8, 115.4 and 61.2 ng ml⁻¹ and increased to 263.8, 328.3, 436.4 and 317.0 ng ml⁻¹ in patients 1, 2, 3 and 4, respectively, following concomitant treatment with propafenone. This corresponds to a decrease of the oral clearance of metoprolol from 2806, 1104, 1204 and 2333 to 527, 423, 318 and 438 ml min⁻¹, respectively, in these four patients. In two of the patients (1 and 3) it is evident that propafenone also reduces the rate of decline of metoprolol concentrations.

In contrast to the results obtained for metoprolol, the concentrations of propafenone were

not affected by simultaneous administration of metoprolol (Figure 2). These four patients had been originally treated with the combination of both drugs and subsequently treatment with metoprolol was stopped. Figure 2 also shows that there are large interindividual differences in the plasma concentrations of propafenone following the same dose of 150 mg three times daily. While in patient 7 maximal concentrations of about 200 ng ml⁻¹ were measured, these were more than 2000 ng ml⁻¹ in patient 8.

Two of the eight patients developed major side effects when the drug combination was given. Patient 5 suffered from severe distressing nightmares and patient 8 from acute left ventricular failure with pulmonary oedema and haemoptysis. These side effects disappeared on reduction of the dose (patient 5) or discontinuation (patient 8) of treatment with metoprolol.

Study B in volunteers

The plasma concentration vs time curves of metoprolol in the six healthy subjects who received either an oral dose of 50 mg metoprolol tartrate alone or 30 min after an oral dose of 150 mg propafenone are shown in Figure 3. All but subject 4 had higher concentrations of metoprolol when they received propafenone additionally.

Figure 1 Steady-state plasma concentrations of metoprolol in patients during a dosing interval when given without (○) and with concomitant propafenone treatment (●). The dosing regimen of metoprolol was 50 mg three times daily, 100 mg twice daily, 100 mg twice daily, and 50 mg three times daily in patients 1, 2, 3 and 4, respectively, and that of propafenone 150 mg three times daily.

Figure 2 Steady-state plasma concentrations of propafenone in patients during a dosing interval of 6 h without ($\circ$) and with concomitant metoprolol treatment ($\bullet$). The dosing regimen of propafenone was 150 mg three times daily and that of metoprolol 50 mg three times daily.

Figure 3 Plasma concentrations of metoprolol in six healthy volunteers following a single oral dose of 50 mg. Plasma concentrations when only metoprolol was administered ($\circ$) and when the volunteers received in addition a single dose of 150 mg propafenone 30 min prior to the dose of metoprolol ($\bullet$).

The pharmacokinetic parameters calculated from the curves of Figure 3 are shown in Table 2. It is evident that the mean AUC increased and the oral clearance decreased in the presence of propafenone. The terminal half-life also showed a tendency to increase. This effect, however, could not be verified statistically.

The pharmacokinetic parameters of propafenone showed marked interindividual variations (Table 3). In two of the subjects propafenone was barely detectable in plasma following a single oral dose. In the four remaining subjects no clear evidence for a drug interaction of metoprolol on the kinetics of propafenone can be obtained.

Table 2 Pharmacokinetic parameters of metoprolol in six healthy subjects following a single oral dose of 50 mg of metoprolol alone and following simultaneous administration of a single dose of 150 mg propafenone 30 min prior to the dose of metoprolol

Subject	Metoprolol			Metoprolol and propafenone		
	AUC (ng ml ⁻¹ h)	t _{1/2} (h)	CL/F (l min ⁻¹)	AUC (ng ml ⁻¹ h)	t _{1/2} (h)	CL/F (l min ⁻¹)
1	264.7	2.33	3.15	511.2	6.81	1.63
2	208.4	2.35	4.00	749.7	5.14	1.11
3	842.6	3.55	0.99	1068.4	3.71	0.78
4	690.3	5.62	1.21	598.1	4.40	1.39
5	327.4	2.15	2.55	887.8	2.86	0.94
6	417.5	2.00	2.00	898.3	2.78	0.93
Mean	458.4	3.00	2.32	785.6*	4.28	1.13*
s.d.	253.1	1.40	1.15	207.3	1.53	0.32

*Statistically significant differences ($P < 0.05$) between both treatments.

Table 3 Pharmacokinetic parameters of propafenone in six healthy subjects following a single oral dose of 150 mg propafenone alone and following simultaneous administration of a single dose of metoprolol (50 mg) 30 min after the propafenone dose

Subject	Propafenone			Propafenone and metoprolol		
	AUC (ng ml ⁻¹ h)	t _{1/2} (h)	CL/F (l min ⁻¹)	AUC (ng ml ⁻¹ h)	t _{1/2} (h)	CL/F (l min ⁻¹)
1	—	—	—	—	—	—
2	—	—	—	—	—	—
3	492	2.79	5077	268	1.19	9321
4	3387	11.67	738	2500	9.93	1000
5	134	1.38	18615	361	2.34	6921
6	241	3.33	10361	181	3.53	13843
Median	188	2.09	2908	225	1.77	3961

In subjects 1 and 2 most plasma concentrations of propafenone were below the detection limit (< 10 ng ml⁻¹) and it was not possible to estimate pharmacokinetic parameters properly.

The results obtained for the β -adrenoceptor-blocking activity of metoprolol measured in the same subjects are shown in Figure 4. There was a more than 20% reduction of exercise-induced tachycardia 1.5 h following an oral dose of 50 mg metoprolol tartrate. Thereafter, the effect slowly declined over the investigation period of 12 h.

Analysis of the data by ANOVA indicated that in the presence of propafenone the time course of effect from 0 to 12 h is significantly different from that of metoprolol alone ($P < 0.04$). These differences are more pronounced if only the values from 6 to 12 h are evaluated ($P < 0.029$). Using Student's *t*-test significant differences were found 6, 8 and 12 h but not at 1.5 and 3 h following drug administration. Exercise tests performed following a single dose of 150 mg propafenone alone showed no statistically significant reduction of exercise induced tachycardia.

Discussion

The results of this study show that there is a marked effect of propafenone on the steady-state plasma levels of metoprolol. In the four patients monitored, steady-state levels increased two to five times when propafenone was added. Although these results were obtained under usual clinical settings and might be influenced by several other conditions such as concomitant treatment with other drugs (see Table 1), diagnostic procedures etc., there is strong evidence that these changes are mainly the results of concomitant propafenone therapy. The clinical symptoms noted in two of these patients (nightmares and cardiac failure) might result, too, from the marked elevation of metoprolol levels since they disappeared by reducing the dose or stopping metoprolol treatment.

Figure 4 Time-course of reduction of exercise induced tachycardia (% of the pretreatment value; mean $\pm$ s.e. mean of six healthy subjects) following a single dose of 50 mg metoprolol (open columns), and following additional administration of a single dose of 150 mg propafenone (hatched columns). Stars indicate statistically significant differences ($P < 0.05$) between both treatments.

Studies in the six healthy volunteers following administration of single oral doses of both drugs clearly demonstrate an about two-fold reduction of oral clearance of metoprolol following simultaneous administration of propafenone. Moreover, the β -adrenoceptor blocking effect of metoprolol is more pronounced following this drug combination. Since the concentration-response curve of metoprolol as measured by reduction of exercise-induced tachycardia is shallow (Sklar *et al.*, 1982), one would expect only a small enhancement of effect when plasma concentrations are raised two-fold. For example, Sklar *et al.* (1982) measured an about 16% and 20% reduction of exercise-induced tachycardia at metoprolol concentrations of 50 and 100 ng ml⁻¹, respectively.

The mechanism of this drug interaction has to be further explored. It is likely that the increase in metoprolol plasma levels results from a re-

duced first-pass metabolism and from a reduced systemic clearance of metoprolol in the presence of propafenone. Both drugs are oxidised by the cytochrome P-450 system in the liver (Regårdh & Johnsson, 1980; Hege *et al.*, 1984) and inhibition of the metabolism of metoprolol by propafenone is most likely.

The more marked effect seen by the patients during chronic therapy compared with that observed in volunteers following single doses could result from accumulation of propafenone and its metabolites when administered continuously (Kates *et al.*, 1985). It was shown that the first-pass metabolism of propafenone is saturable which causes the plasma levels to increase more than proportionally by increasing the dose and during chronic therapy (Hollmann *et al.*, 1983; Connolly *et al.*, 1983). In this situation one would expect a higher inhibitory effect at steady-state than following a single dose.

Despite the marked changes in the pharmacokinetics of metoprolol during simultaneous administration of propafenone, it seems that the kinetics of propafenone during chronic therapy are not affected by metoprolol. The study performed in healthy volunteers revealed large intersubject differences in the plasma levels of propafenone following a single oral dose of 150 mg (Table 3). In two of the subjects propafenone was barely detectable in plasma which most likely indicates extensive hepatic extraction. From the results obtained in the remaining four subjects no definite conclusion can be drawn whether or not metoprolol affects the kinetics of propafenone.

In summary, the simultaneous administration of propafenone to patients on therapy with metoprolol can cause a marked increase in the plasma levels of metoprolol. Although the therapeutic concentration ratio of metoprolol is large, the pronounced rise of plasma concentrations might cause severe side effects in some patients. It seems necessary, therefore, to reduce the dose of metoprolol when propafenone is administered simultaneously.

References

- Briant, R. H., Dorrington, R. E., Ferry, D. G. & Paxton, J. W. (1983). Bioavailability of metoprolol in young adults and the elderly, with additional studies on the effects of metoclopramide and probanthine. *Eur. J. clin. Pharmac.*, **25**, 353-356.
- Brode, E., Sachse, R. & Hoffmann, H. D. (1982). Untersuchungen zur Analytik von Propafenon mittels interner Analogstandardisierung. *Arznei-mittel-Forsch. (Drug Res.)*, **32**, 1-6.
- Connolly, S., Lebsack, C., Winkle, R. A., Harrison, D. C. & Kates, R. E. (1984). Propafenone disposition, kinetics in cardiac arrhythmias. *Clin. Pharmac. Ther.*, **36**, 163-168.
- Connolly, S. J., Kates, R. E., Lebsack, C. S., Harrison, D. C. & Winkle, R. A. (1983). Clinical pharmacology of propafenone. *Circulation*, **68**, 589-596.
- Hege, H. G., Hollmann, M., Kaumeier, S. & Lietz, H. (1984). The metabolic fate of ²H-labelled pro-

- pafenone in man. *Eur. J. Drug Metab. Pharmacokin.*, **9**, 41-55.
- Hollmann, M., Brode, E., Hotz, D., Kaumeier, S. & Kehrhahn, O. H. (1983). Investigations on the pharmacokinetics of propafenone in man. *Arzneimittel-Forsch. (Drug Res.)*, **33**, 763-770.
- Kates, R. E., Yee, Y. G. & Winkle, R. A. (1985). Metabolite cumulation during chronic propafenone dosing in arrhythmia. *Clin. Pharmac. Ther.*, **37**, 610-614.
- Lüderitz, B. (1986). Wirkungsspektrum der Beta-rezeptoren-blockade bei Herzrhythmusstörungen. *Z. Kardiol.*, **7** (Suppl.), 9.
- Regårdh, C. G. & Johnsson, G. (1980). Clinical pharmacokinetics of metoprolol. *Clin. Pharmacokin.*, **5**, 557-569.
- Siddoway, L. A., Roden, D. M. & Woosely, R. L. (1984). Clinical pharmacology of propafenone: Pharmacokinetics, metabolism and concentration-response relations. *Am. J. Cardiol.*, **54**, 9D-12D.
- Sklar, J., Johnston, G. D., Overlie, P., Gerber, J. G., Brammell, H. L., Gal, J. & Nies, A. S. (1982). The effects of a cardioselective (metoprolol) and a non-selective (propranolol) beta-adrenergic blocker on the response to dynamic exercise in normal men. *Circulation*, **65**, 894-895.

(Received 19 December 1986,
accepted 15 April 1987)