Interaction between sotalol and an antacid preparation

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Aims The aim of the study was to investigate the pharmacokinetic interaction between sotalol and antacids, and its pharmacodynamic relevance.

Methods In a randomized cross-over design with three treatment groups, six healthy volunteers received orally either 160 mg of sotalol alone (phase 1), or 160 mg sotalol plus 20 ml of a suspension of an antacid (MAH; magnesium hydroxide (1200 mg) and aluminium oxide (1800 mg)) (phase 2) or 160 mg sotalol plus the antacid given 2 h after sotalol administration (phase 3). Heart rate and plasma sotalol concentrations were measured before and 1, 2, 3, 4, 6, 8, 12 and 24 h after sotalol administration. Urinary sotalol excretion was measured for 24 h after sotalol application.

Results $C_{\max}$ of sotalol decreased from $1.22 \pm 0.22 \text{ mg l}^{-1}$ (phase 1) to $0.89 \pm 0.29 \text{ mg l}^{-1}$ (phase 2) and increased again to $1.27 \pm 0.18 \text{ mg l}^{-1}$ in phase 3. A similar significant change was noted in AUC ($15.6 \pm 2.75 \text{ mg l}^{-1}$, $12.3 \pm 3.04 \text{ mg h l}^{-1}$ and $15.0 \pm 2.06 \text{ mg l}^{-1}$) and in the amount of cumulative urinary excretion ($79.2 \pm 11.1 \text{ mg}$, $72.1 \pm 11.2 \text{ mg}$ and $80.6 \pm 7.9 \text{ mg}$), respectively. $t_{\max}$ and elimination half-life ($t_{1/2,z}$) of sotalol remained unchanged in the presence of MAH. After combined administration with MAH, the area under the heart rate curve of sotalol was reduced between 0 and 4 h when compared across treatments.

Conclusions Combined administration of sotalol and MAH decreased the serum sotalol levels. The interaction can be avoided by a two hour interval between application of these drugs.

Keywords: sotalol, antacids, pharmacokinetics, pharmacodynamics, interaction

Introduction

Cardiac arrhythmias occur with a high incidence in Western countries. However, the cardiac arrhythmia suppression trials, CAST 1 and 2, have shown that class I antiarrhythmic agents do not exert beneficial effects on mortality and morbidity in patients with arrhythmias [1, 2]. In contrast, there is evidence that β -adrenoceptor blockers and class III antiarrhythmic drugs are currently the best choice [3–5]. For instance, sotalol reduced mortality in patients with ventricular arrhythmias [4]. Clinically important adverse effects of sotalol like proarrhythmias are associated with lengthening of the QTc interval [6–8]. A correlation between the serum sotalol concentrations and prolongation of the QTc interval has been reported [9–11]. Thus, alterations in serum sotalol concentrations can influence clinical effects of sotalol treatment. Sotalol is not metabolized in the liver and increased plasma concentrations have been reported in patients with renal failure [12]. Food also influences the relative bioavailability of sotalol and milk decreases serum sotalol concentrations [13]. Pharmacokinetic interactions have been reported between classical β -adrenoceptor blockers like propranolol and widely used antacid drugs [14, 15]. Previous studies with sotalol have indicated a

significant reduction in $C_{\max}$ when applying a magnesium cation containing preparation [16]. However, data are lacking on the pharmacodynamic relevance of this interaction. Hence, given the clinical importance and widespread use of sotalol and antacids, we investigated the pharmacokinetic interaction between these compounds and also measured heart rate as an easily accessible functional parameter.

Methods

Study design

Six healthy male volunteers (age range: 24 to 30 years; weight range: 63 to 80 kg) consented freely to participate in the study, which was approved by the local Ethics Committee. Subjects were in good health as assessed by history, appropriate laboratory tests, and physical examination. No concomitant medication was allowed during the study. A randomized, cross-over experimental design with three treatments was followed. The treatments were separated by a wash-out period of 1 week. The subjects received orally either 160 mg of sotalol (Sotalex[®]; ($\pm$)-sotalol, Bristol-Myers Squibb, Munich, Germany) (Phase 1) or 160 mg sotalol plus 20 ml MAH suspension (Maalox[®], Rorer, Cologne, Germany, 1200 mg magnesium hydroxide and 1800 mg aluminium oxide in 20 ml, MAH) (Phase 2) or 160 mg sotalol and 20 ml MAH 2 h later (Phase 3) with 100 ml water. The volunteers

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fasted overnight before administration of the drugs and until 4 h after drug administration.

Sampling, determination of sotalol and haemodynamic measurements

An intravenous cannula was inserted into a forearm vein and blood specimens were drawn before and 1, 2, 3, 4, 6, 8, 12, and 24 h after sotalol application. Blood was centrifuged at 2740 g for 15 min. Serum was stored at -80°C until analysis. Sotalol concentrations were measured by h.p.l.c. with u.v.-detection as described earlier with minor modifications [17]. The limit of quantitation for sotalol was $0.05\text{ }\mu\text{g ml}^{-1}$ and the intra-assay and inter-assay variation were 4.5% and 4.4%, respectively. Urine was collected for 24 h after sotalol application and an aliquot of 1 ml was stored at -80°C until analysis. Heart rate was recorded after a 5 min rest in the supine position as a mean of three measurements with a Visomat (Hestia, Mannheim, Germany) each time before the blood sample was taken.

Adsorption study in vitro

Sotalol tablets of 80 mg, 160 mg and 320 mg ($2 \times 160\text{ mg}$) were dissolved into 100 ml of 0.1 M HCl for 30 min at 37°C . 20 ml of the MAH suspension was added and agitated for another 30 min. 500 μl samples were drawn before and after MAH addition, centrifuged for 10 min at 2740 g and the supernatant was analyzed for sotalol with the h.p.l.c. system.

Data analysis and statistics

Data are given as arithmetic means $\pm$ s.d.. Pharmacokinetic parameters were calculated using Topfit 2.0 software [18]. Plasma elimination half life ($t_{1/2,z}$) was determined from the linear part of the concentration-time curve on a semilog graph. The area under the plasma drug concentration curve (AUC) was calculated by the linear trapezoidal rule and the

area to infinite time added by integration (C_t/λ_z), where C_t is the last drug concentration value and λ_z the elimination rate constant calculated for the equation $\ln 2/t_{1/2}$. The area under the effect curve (differences of heart rate *vs* heart rate of predrug value) was calculated with Topfit 2.0. Statistical significance of the differences was calculated by Wilcoxon's matched pairs test. $P < 0.05$ was considered to be significant. The statistical software package SPSS 6.1 was used for analysis of the data.

Results

Pharmacokinetics

Application of 160 mg sotalol alone led to a maximum plasma concentration (C_{max}) of $1.22 \pm 0.22\text{ mg l}^{-1}$ 3 h after administration (Figure 1). Simultaneous administration of MAH reduced maximum sotalol plasma concentration to $0.89 \pm 0.29\text{ mg l}^{-1}$ (Figure 1). Two hours interval in application of both drugs revealed no influence of MAH on sotalol maximum plasma concentrations ($1.27 \pm 0.18\text{ mg l}^{-1}$) (Figure 1). AUC values were reduced by 21% from $15.6 \pm 2.75\text{ mg l}^{-1}$ (Phase 1) to $12.3 \pm 3.04\text{ mg l}^{-1}$ (Phase 2) by concurrent MAH application. AUC values did not change when the application of sotalol and MAH was separated by 2 h ($15.0 \pm 2.06\text{ mg l}^{-1}$, Phase 3). About 49% ($79.2 \pm 11.1\text{ mg}$) of the 160 mg sotalol dose was excreted in the urine in 24 h. Concurrent MAH application decreased urinary excretion by 9% to $72.1 \pm 11.2\text{ mg}$ ($P < 0.05$). Interval application did not influence urinary excretion ($80.6 \pm 7.9\text{ mg}$). t_{max} and $t_{1/2,z}$ values remained unchanged (Table 1).

Adsorption study in vitro

Table 2 contains data on the *in vitro* adsorption of sotalol to the MAH suspension. MAH suspension bound approximately 12% of the dissolved 80 mg, 160 mg or 320 mg sotalol tablets. This is in the same range as the reduction in AUC (21%) or in urinary excretion of sotalol (9%) of the *in vivo* study.

Pharmacodynamics

The AUC (0, 4 h) for the differences in heart rate *vs* predrug value for each subject were smaller during concurrent application of sotalol and MAH ($32 \pm 15.0\text{ beats min}^{-1}$) than during sotalol alone ($56.2 \pm 35.1\text{ beats min}^{-1}$) or when there was a 2 h interval in application of both drugs ($49.1 \pm 32.2\text{ beats min}^{-1}$) (Wilcoxon's test for matched pairs). The AUC (0, 4 h) for the difference of heart rate *vs* predrug value of each subject did not differ between treatment phases (see Table 3).

Discussion

Sotalol is an effective antiarrhythmic agent in patients with supraventricular and ventricular arrhythmias and is therefore extensively used in Europe and in the United States. In patients with normal renal function the minimally effective antiarrhythmic dose of orally administered sotalol is 80 to 160 mg day^{-1} in a single or in two equal doses [19]. In

Figure 1 Time course of sotalol plasma concentrations following three different treatments: phase 1 (▲) 160 mg sotalol alone, phase 2 (□) 160 mg sotalol and concurrent application of 20 ml MAH suspension, phase 3 (◆) 160 mg sotalol and administration of 20 ml MAH suspension 2 h later, $n = 6$. Data are given as mean $\pm$ s.d.

Table 1 Pharmacokinetic parameters of sotalol in six healthy volunteers after three different treatments: phase 1, 160 mg sotalol alone; phase 2, 160 mg sotalol with simultaneous application of 20 ml MAH suspension; phase 3, 160 mg sotalol with administration of 20 ml MAH suspension 2 h later. Results are given as means $\pm$ s.d., $n=6$.

	Phase 1	Phase 2	Phase 3	Mean of differences	
				Phase 1–2 (95% CI)	Phase 3–2 (95% CI)
$C_{\max}$ (mg l ⁻¹)	1.22 $\pm$ 0.22	0.89 $\pm$ 0.29	1.27 $\pm$ 0.18	0.33 (0.19–0.48)★	0.36 (0.08–0.64)★
AUC (mg h l ⁻¹)	15.6 $\pm$ 2.75	12.3 $\pm$ 3.04	15.0 $\pm$ 2.06	3.22 (0.08–6.37)★	2.67 (0.96–4.40)★
$t_{\max}$ (h)	3.3 $\pm$ 1.4	3.3 $\pm$ 1.5	3.8 $\pm$ 1.2	0 (–0.66–0.66)	0.5 (–0.08–1.07)
$t_{1/2,z}$ (h)	8.06 $\pm$ 1.01	9.22 $\pm$ 2.41	7.75 $\pm$ 0.93	1.54 (–3.26–0.18)	–1.47 (–3.53–0.60)

★indicates significant differences ($P<0.05$) (Wilcoxon's test for matched pairs).

Table 2 Amount of sotalol adsorbed by MAH *in vitro*. Figures in parenthesis indicate number of experiments.

Sotalol (mg)	Amount adsorbed by MAH in vitro (mg)	% of adsorbed sotalol by MAH in vitro
80	7.9 $\pm$ 0.9 (3)	9.9 $\pm$ 1.1
160	21.1 $\pm$ 2.9 (3)	13.1 $\pm$ 1.8
320	41.7 $\pm$ 2.3 (3)	13.0 $\pm$ 0.7

Table 3 Area under the effect curve of differences of heart rates *vs* predrug value of each subject during treatments. Values are means $\pm$ s. d., $n=6$.

	Area under the effect curve 0–24 h (beats h min ⁻¹)	Area under the effect curve 0–4 h (beats h min ⁻¹)
Phase 1	226 $\pm$ 73.7	46.3 $\pm$ 16.2
Phase 2	139 $\pm$ 65.0	32.0 $\pm$ 15.0★
Phase 3	246 $\pm$ 194	49.1 $\pm$ 32.2

★significantly different from phase 1 and phase 3 (Wilcoxon's test for matched pairs).

order to facilitate comparison with previous work [13, 16] a single oral dose of 160 mg sotalol was used in the present study. Gastrointestinal diseases with an aetiology of a disbalance of aggressive and defensive factors are still often treated with antacid drugs. Maalox® is the most frequently used antacid in Germany [15]. Recommended doses are 10 or 20 ml four times a day up to 20 ml every 3 h [20]. It is reasonable to assume that a number of patients are taking at the same time antiarrhythmics and antacid drugs.

In the present study concurrent application of sotalol and MAH decreased $C_{\max}$ by 26%, AUC by 21% and 24 h urinary excretion by 9% compared with application of sotalol alone. $t_{\max}$ and $t_{1/2,z}$ remained unchanged in all treatment phases. $t_{\max}$ of sotalol of about 3 h was in agreement with previous publications [12, 16, 21]. Concurrent administration of antacids did not change $t_{\max}$ values. This fits well with results obtained by other investigators that antacids do not alter the velocity of sotalol absorption [16]. In addition, concurrent MAH administration had no influence on the elimination kinetics of sotalol. The calculated sotalol plasma half-lives of about 8 to 10 h are

compatible with plasma half-lives of 7 to 18 h in patients with normal renal function as reported elsewhere [12, 21]. 49% of the dose of sotalol was found in the urine in 0–24 h after administration. A similar percentage excretion (54%) was reported previously [22]. Results concerning pharmacokinetic interactions between β -adrenoceptor blockers and antacids were reported in earlier studies [14, 16]. Those data showed that concurrent administration of 160 mg sotalol and 15 mmol magnesium cations diminished $C_{\max}$ by 16% whereas 15 mmol aluminium cations did not change $C_{\max}$. AUC remained unchanged either with magnesium or aluminium cations [16]. Our data revealed a greater decrease of $C_{\max}$ by 26% and a 21% decrease of AUC. One possible reason would be that we used a combination of 14 mmol magnesium and 9 mmol aluminium cations. It is generally assumed that a decrease in $C_{\max}$ and AUC can be caused either by reduced absorption or altered metabolism of a drug. However, since no metabolites of sotalol have been detected or identified [12], the observed reduction in $C_{\max}$ and AUC in our study is most probably due to diminished absorption of sotalol. The *in vitro* adsorption study demonstrated clearly that the MAH suspension binds about 12% of the dissolved sotalol (Table 2). *In vivo*, the reduced sotalol urinary excretion by 9% suggests that sotalol is not completely absorbed in the gastrointestinal tract in the presence of the MAH suspension. Consequently, MAH suspension reduces the relative bioavailability of sotalol.

In the present study, heart rate was measured as an easy accessible functional parameter for the clinical effect of sotalol. The data suggest that the negative chronotropic effect of sotalol was reduced up to 4 h post application following concurrent administration of MAH. It is suggested that this is caused by the reduced serum levels of sotalol. Interval application between sotalol and MAH avoids the interaction. However, although a placebo control for sotalol is not required for the pharmacokinetic interaction a placebo control for the haemodynamic measurements would have facilitated the interpretation of our haemodynamic findings which therefore should be regarded as preliminary. Further studies are required to definitely show that this leads to a pharmacodynamically relevant interaction in patients. However, we feel that this work is a starting point to look more closely into pharmacodynamic interactions.

It is generally assumed that plasma levels of sotalol correlate with its antiarrhythmic efficacy. Thus, reduced levels of sotalol by drug interaction could reduce the clinical effect of the drug and increase the cardiac risk of patients

not measurable in healthy volunteers. Also patients with chronic simultaneous application of sotalol and antacids like MAH probably will have lower plasma steady state levels of sotalol. Thus, alterations in the bioavailability of sotalol could influence clinical efficacy and increase the risk of adverse effects. Precautions should be observed by changing the treatment protocol of drug administration. In summary, concurrent administration of sotalol and MAH cause both pharmacokinetic and pharmacodynamic interactions. These interactions can be overcome by interval application of both compounds.

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