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THE EFFECT OF ANTACID, METOCLOPRAMIDE, AND PROPANTHELINE ON THE BIOAVAILABILITY OF METOPROLOL AND ATENOLOL

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ABSTRACT

Concomitant administration of antacid increased the maximum concentration (Cp_{max}) and the area under the plasma concentration–time curve (AUC) of 100 mg oral dose of metoprolol by 25 per cent ($p < 0{\cdot}05$) and 11 per cent ($p < 0{\cdot}1$) respectively. For atenolol the opposite effect was observed and Cp_{max} and AUC were decreased by 37 and 33 per cent respectively ($p < 0{\cdot}02$). In both cases the antacid did not affect the time–course of the drug in the plasma. Pretreatment with metoclopramide did not affect the time-course of atenolol in the plasma or its bioavailability. Propantheline prolonged the absorption phase of atenolol and the time of peaking (t_{max}) was shifted from 2·1 to 4·5 h. Cp_{max} of atenolol was essentially unchanged by propantheline pretreatment while the AUC was increased by 36 per cent. It is concluded that the negative effect of the antacid on the bioavailability of atenolol is caused by a reduction in the *in vivo* dissolution rate due to increased gastric pH. The positive effect of propantheline might be due either to more efficient absorption of atenolol in the upper part of the intestine or more extensive dissolution of the drug as a result of prolonged contact with gastric juice or a combination of these factors.

KEY WORDS Metoprolol Atenolol Antacid Interaction Gastric emptying

INTRODUCTION

Concomitant administration of antacids has been found to interact with a number of different drugs in the gastrointestinal tract.[1,2] The results of these interactions depend to a large extent on the individual drugs with reduced, increased, and also unaffected absorption being reported in association with antacid therapy. At present, however, there seems to be no general method of predicting if and in what way an antacid will affect the gastrointestinal absorption of specific drugs.

A reduction in the extent of bioavailability of propranolol by about 50 per cent in association with concomitant intake of an antacid has been reported by Dobbs *et al.*,[3] but apart from this study little attention has been given to interactions

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between antacids and β-adrenoceptor antagonists. The findings of Dobbs *et al.*[3] raises the question of whether the observed interaction is unique for propranolol or for its formulation or whether it would also occur with other β-adrenoceptor antagonists because of their physico-chemical similaritites to propranolol.

In this paper we have studied the effect of an aluminium-magnesium hydroxide-containing antacid on the bioavailability of metoprolol and atenolol. During fasting conditions about 50 per cent of a single oral therapeutic dose of these drugs is available systemically but their availability is controlled by different mechanisms. Metoprolol is completely absorbed from the gastrointestinal tract but about 50 per cent is removed by the first-pass effect.[4, 5] Atenolol, on the other hand, is only absorbed by about 50 per cent from the gut.[6] Due to the different absorption characteristics food and antacid might interfere differently with the absorption of these two drugs.

The aim of the present study is to clarify the potential influence of antacid on the bioavailability of metoprolol and atenolol. Since a substantial decrease in the bioavailability of atenolol was observed when taken together with the antacid the effects of metoclopramide and propantheline on the bioavailability of atenolol were studied separately. Metoclopramide increases and propantheline decreases the rate of gastric emptying and these drugs were included in the study to find out to what extent a change in gastric motility, potentially caused by the antacid,[7] would affect the bioavailability of atenolol.

SUBJECTS AND METHODS

The study was approved by the ethics committee of the University of Gothenburg.

Interaction with antacid

Six healthy male volunteers 23–27 years of age took part in the study. The subjects had fasted for at least 10 h prior to the drug administration. One ordinary 100 mg tablet of metoprolol (Seloken® 0·1 g: AB Hässle, Batch No. OK 132) or atenolol (Tenormin®: ICI Ltd, Batch No. HN 503) was administered alone and together with 30 ml of an antacid suspension in randomized order approximately 1 week apart. The antacid (Novalucol forte: Batch No. DK 198) contains a mixture of aluminium and magnesium hydroxide and aluminium hydroxide–magnesium carbonate. Ten ml of the suspension binds 52·5 mmol HCl.

The drugs were taken together with 100 ml of water immediately followed by the antacid. After 3 h the subjects were allowed a light standardized lunch and after 6 h a glass of milk and a sandwich. After 8 h there was no restriction in diet. Blood samples were drawn immediately before the administration of the tablet and then after 0·5, 1, 1·5, 2, 3, 4·5, 6, and 8 h for both drugs and also after 24 and 25 h for atenolol. The plasma was stored at −20 °C until analysis.

The plasma concentrations of metoprolol were determined by gas chromatography according to Ervik.[8] Atenolol was extracted from the plasma by methylene chloride containing 3 per cent heptafluorobutanol. After evaporation of the organic solvent, atenolol was reacted with trifluoroacetic anhydride in diethylether. The organic solvent and the excess of reagent was evaporated and the derivative was dissolved in toluene and determined by gas chromatography with electron capture detection.[9]

Effect of gastric emptying rate on the absorption of atenolol

Another group of six healthy male volunteers, 23–27 years of age, were given one atenolol tablet either alone or together with 25 mg of metoclopramide (Primperan® mixture 1 mg ml^{-1}: Lundbeck, Batch No. D 2049) or 30 mg of propantheline (Pro-Banthine® 15 mg tablet: Searle, Batch No. 678653). The experiments were carried out in randomized order at an interval of about 1 week. The subjects had fasted for at least 10 h prior to drug administration. The atenolol tablet was taken together with 100 ml water. Metoclopramide and propantheline were administered 1 and 1·5 h, respectively, before the intake of the atenolol tablet. The protocol for food intake and blood sampling was the same as for atenolol in the interaction study with antacid.

Disintegration test

The time taken for disintegration of the tablets was determined in water and in the antacid suspension according to U.S.P. XIX with discs.

In vitro *dissolution rates*

The rate of dissolution of metoprolol and atenolol from Seloken® and Tenormin® tablets was compared in water and in a suspension of water and Novalucol forte at 37 °C. A tablet was placed on a stainless gauze wire 2 cm above the bottom of a 600 ml beaker. The beaker was filled with either 300 ml of water, or a suspension of 270 ml of water and 30 ml of Novalucol forte, pH ~ 8·5. The liquid was stirred by a propeller, 45 × 15 mm, located 2 cm above the tablet. The stirring speed was 50 rev min^{-1}. The amount of drug dissolved in the suspension was determined after 5, 10, 15, 20, 30, 40, and 60 min in two different ways to quantify the adsorption of atenolol to the antacid

A: 1 ml of concentrated HCl was added to 5 ml of the suspension. The resulting clear solution was diluted with H_2O to 10 ml and assayed spectrophotometrically.
B: The suspension was centrifuged and 5 ml of the supernatant was diluted with 1 ml of concentrated HCl and H_2O to 10 ml. The concentrrtion in the liquid phase was determined spectrophotometrically.

Data analysis

The effect of the antacid on the extent of bioavailability of metoprolol and atenolol was determined in each subject from the ratio of the area under the

plasma concentration–time curve (AUC_τ) obtained with and without concomitant antacid administration.

The linear trapezoidal rule was used to determine the AUC from time 0 to the time of the second sample after the maximum concentration. The log-linear trapezoidal rule[10] was used from this time to the time of the last sample and the remaining area to time infinity was determined by dividing the concentration of the last sample by the terminal rate constant.

Student's *t*-test for paired observations was used to estimate the significance of the effect of the antacid, metoclopramide, and propantheline on the absorption characteristics and elimination half-lives. The effect was considered significant at the $p < 0{\cdot}05$ level.

RESULTS AND DISCUSSION

The mean plasma concentration versus time curves of metoprolol and atenolol when administered alone and together with antacid are shown in Figures 1 and 2, respectively. The corresponding individual absorption characteristics and elimination half-lives are given in Tables 1 and 2.

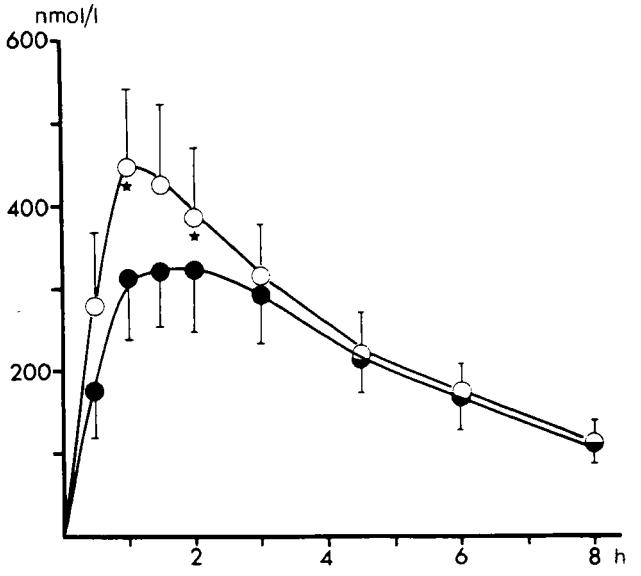

Figure 1. The effect of concomitant administration of antacid on the plasma levels of metoprolol. (●) Metoprolol alone; (○) Metoprolol + antacid. Mean values ± S.E.M. are indicated. $n = 6$. (*) $p < 0{\cdot}05$

Concomitant administration of the antacid increased the maximum concentration, Cp_{max}, of metoprolol by 25 per cent ($p < 0{\cdot}05$) and the area under the plasma concentration *versus* time curve, AUC_τ, by 11 per cent ($p < 0{\cdot}1$). The antacid had no apparent effect on the time of peaking, t_{max}, or on the elimination half-life, $T_{\frac{1}{2},\beta}$, of metoprolol.

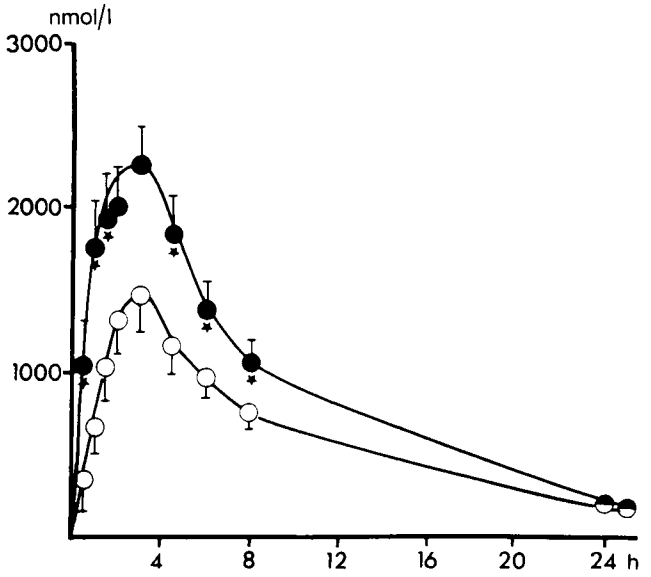

Figure 2. The effect of concomitant administration of antacid on the plasma levels of atenolol. (●) Atenolol alone; (○) Atenolol + antacid. Mean values ± S.E.M. are indicated. $n = 6$. (*) $p < 0{\cdot}05$

Table 1. Individual absorption and elimination characteristics of metoprolol administered alone and together with an antacid

Subject	Cp_{max} (nmol l^{-1}) Alone	Antacid	t_{max} (h) Alone	antacid	AUC_{∞} (nmol h l^{-1}) Alone	Antacid	$T_{\frac{1}{2}\beta}$ (h) Alone	Antacid
L. A.	563	624	1·0	1·0	2849	3485	3·3	4·1
L. S.	611	782	2·0	1·0	4143	4288	3·6	3·2
B. A.	206	257	1·0	1·0	857	989	2·6	2·6
M. L.	162	299	1·5	1·0	1259	1505	3·8	3·3
E. B.	412	584	1·5	1·5	2935	3457	3·8	3·3
C. J.	253	213	3·0	2·0	1648	1484	2·9	2·7
$\bar{M}$	368	460	1·7	1·3	2282	2534	3·3	3·2
S.E.M.	78	96	0·3	0·2	506	559	0·2	0·2
p	$<0{\cdot}05$				$<0{\cdot}1$			

Administration of the antacid suspension along with the atenolol tablet significantly reduced Cp_{max} and AUC, by an average of 37 and 33 per cent, respectively ($p < 0{\cdot}02$), compared with administration of atenolol alone, but the antacid had no significant effect on t_{max} or $T_{\frac{1}{2},\beta}$ of atenolol.

According to these results concomitant administration of the antacid tends to increase the fraction of metoprolol systemically available and leads to a substantial reduction in the systemic availability of atenolol whereas it has

Table 2. Individual absorption and elimination characteristics of atenolol administered alone and together with an antacid

Subject	Cp_{max} (μmol l^{-1})		t_{max} (h)		AUC_∞ (μmol h l^{-1})		$T_{\frac{1}{2}\beta}$ (h)	
	Alone	Antacid	Alone	Antacid	Alone	Antacid	Alone	Antacid
L. A.	2·77	1·82	4·5	3·0	34·58	21·57	6·5	7·5
L. S.	1·98	2·20	1·5	3·0	18·87	19·78	7·5	7·5
B. A.	3·02	1·62	3·0	3·0	28·28	16·05	5·8	6·5
M. L.	2·12	1·38	3·0	1·5	23·85	15·94	7·7	8·0
E. B.	2·60	1·21	2·0	0·5	23·11	10·98	6·7	13·0
C. J.	2·82	1·39	3·0	3·0	22·69	17·31	6·2	8·0
$\bar{M}$	2·55	1·60	2·8	2·3	25·23	16·94	6·7	8·4
S.E.M.	0·17	0·15	0·4	0·4	2·24	1·49	0·3	0·9
p	$<0·02$				$<0·02$			

essentially no effect on the rate of absorption and elimination of the two drugs. The potential effect of the antacid on the systemic availability of metoprolol is, however, too low to be of clinical importance. On the other hand, the reduction in the systemic availability of atenolol by an average of 33 per cent (range +5 to −52 per cent) indicates that some patients regularly using antacids would run the risk of having the systemically available dose of atenolol halved and potentially therefore suffering a reduced therapeutic effect. Since antacids are often used without prescription this cause might well be overlooked by the physician in cases of inadequate therapeutic response.

The substantial reduction in the fraction of atenolol available systemically initiated the interaction studies with metoclopramide and propantheline to find out whether a potential change in the rate of gastric emptying caused by the antacid[7] would lead to a reduction of the extent of bioavailability of atenolol. Figure 3 shows that an increase in the rate of gastric emptying induced by metoclopramide pretreatment had essentially no effect on the bioavailability of atenolol. The observed reduction of t_{max} from $2·1 \pm 0·3$ h when atenolol was taken alone to $1·8 \pm 0·3$ h in combination with metoclopramide was not statistically significant.

On the other hand, pretreatment with propantheline caused a significant decrease in the rate of absorption of atenolol and t_{max} was shifted from $2·1 \pm 0·2$ h for atenolol alone to $4·5 \pm 0·4$ h after propantheline pretreatment ($p < 0·02$). Despite the lower absorption rate the maximum concentration of atenolol was, if anything, slightly increased after administration of the anticholinergic drug and the AUC_∞ was increased by 36 per cent ($p < 0·02$).

The effect of propantheline on t_{max} of atenolol is similar to the results obtained with other drugs, for instance propranolol and acetaminophen.[11,12] Unlike atenolol, however, these two drugs are completely absorbed from the gastrointestinal tract and accordingly the anticholinergic agent cannot further increase their bioavailability by increasing the uptake from the gut.

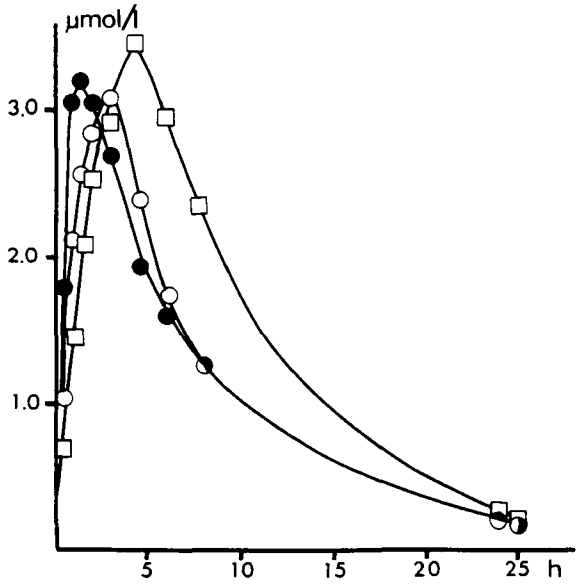

Figure 3. The effect of pretreatment with metoclopramide and propantheline on the plasma levels of atenolol. (○) Atenolol alone; (●) Atenolol + metoclopramide; (□) Atenolol + propantheline. Mean values. $n = 6$.

The positive effect of propantheline on the bioavailability of atenolol is probably secondary to the reduced transit rate of atenolol through the gut. This would favour the fraction available systemically if the drug is more efficiently absorbed in the upper part of the intestine or if the retention time in the stomach increases the dissolution of the drug from the tablet. The latter seems to be the case for atenolol as the Tenormin® tablet is more rapidly dissolved at a lower pH (see below).

The interaction study with metoclopramide and propantheline indicates that the reduction of AUC_x of atenolol caused by concomitant administration of antacid cannot be related to altered rate of gastric emptying. Instead, the antacid probably affects the bioavailability of atenolol by decreasing the dissolution rate of the Tenormin® tablet in the gut. This is indicated in the *in vitro* dissolution test in which only about 50 per cent of the atenolol dose was dissolved during 1 h in the antacid suspension while the dose was dissolved completely during the same time in water (Figure 4). In contrast to atenolol, the dissolution rate of metoprolol was almost the same in water and in the actacid suspension (Figure 4).

The different rates of dissolution of atenolol in water and in the antacid suspension might either be due to adsorption to the aluminium hydroxide gel or a pH-dependent disintegration and/or dissolution of the tablet. However, the adsorption of the β-blocker to the antacid was found to be negligible as the atenolol concentrations in the supernatant and in the acidified solution of the

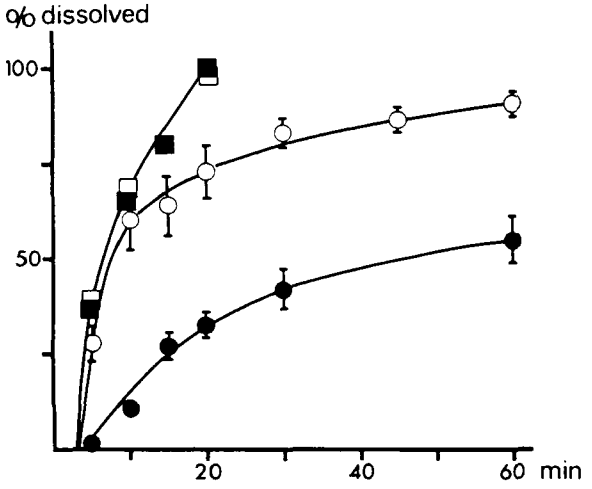

Figure 4. Dissolution rate of metoprolol and atenolol from commercial Selokin® 0·1 g and Tenormin® tablets. (□) Metoprolol in water; (■) Metoprolol in antacid suspension; (○) Atenolol in water; (●) Atenolol in antacid suspension. Mean values ± S.E.M. are indicated. $n = 3$

antacid were almost the same. The time of disintegration of the Tenormin® tablet increased from 2–3 min in water to 5–6 min in the antacid suspension. Considering that this test is a relatively tough test of tablet disintegration, the effect of pH on the disintegration time might be much more pronounced under physiological conditions and might, in addition to the altered dissolution rate, contribute to the decrease in the bioavailability of atenolol although the pH in the stomach might be lower than during the *in vitro* conditions.

The reason why pH influences the disintegration time and dissolution rate of the Tenormin® tablet but has essentially no effect on these properties of the Seloken® tablet is still unclear. Metoprolol and atenolol both have a pK_a of about 9·5 and the pH of the antacid suspension, about 8·5, would have little influence on the ionization and the solubility of these drugs. It is possible, however, that this pH is sufficiently high to decrease the dissolution rate of the atenolol base from the Tenormin® tablet while the dissolution of the neutral metoprolol tartrate from the Seloken® tablet is not affected. Alternatively the Tenormin® tablet might contain some ingredient(s) affecting the disintegration and dissolution of the tablet differently as the pH is changed leading to a substantial reduction in the bioavailability of the drug in association with antacid therapy. Furthermore, the present findings indicate that in other clinical situations like achlorhydria or hypochlorhydria resulting in elevated gastric pH, the bioavailability of atenolol might be lower than in patients with normal production of gastric acid. However, this hypothesis has to be verified clinically.

REFERENCES

1. A. Hurwitz, *Clin. Pharmacokinet.*, **2**, 269 (1977).
2. J. A. Romankiewics and M. M. Reidenberg, *Rational Drug Ther.*, **12**, 1 (1978).

3. J. Dobbs, V. A. Skoutakis, S. R. Acchiardo and B. R. Dobbs, *Curr. Ther. Res.*, **21**, 887 (1977).
4. G. Johnson, C.-G. Regardh and L. Sölvell, *Acta Pharmacol. Toxicol.*, **36**, (Suppl. V), 31 (1975).
5. L. Jordö, P. O. Attman, M. Aurell, L. Johansson, G. Johnsson and C.-G. Regårdh, *Clin. Pharmacokinet.*, **5**, 169 (1980).
6. P. R. Reeves, J. McAinsh, D. A. D. McIntosh and M. J. Winrow, *Xenobiotica*, **8**, 313 (1978).
7. A. Hurwitz, R. G. Robinson, S. Tribhawan, F. C. Whittier and W. F. Herrin, *Gastroenterology*, **71**, 268 (1976).
8. M. Ervik, *Acta Pharmacol. Toxicol.*, **36** (Suppl. V), 136 (1975).
9. M. Ervik, K. Kylberg-Hanssen and P. O. Lagerström, *J. Chromat. Biomed. Appl.*, **182**, 371 (1980).
10. K. C. Yeh and K. C. Kwan, *J. Pharmacokinet. Biopharm.*, **6**, 79 (1978).
11. C. M. Castleden, C. F. George and M. D. Short, *Br. J. Clin. Pharmacol.*, **5**, 121 (1978).
12. W. Nimmo, R. C. Heading, P. Tothill and L. F. Prescott, *Br. Med. J.*, **1**, 587 (1973).