Pharmacodynamic without pharmacokinetic interaction between cicloprolol, a partial β_1 -adrenoceptor agonist, and digoxin in healthy subjects

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1 Cicloprolol is a partial β_1 -adrenoceptor agonist considered for the treatment of patients with coronary artery disease and impaired left ventricular function. In such patients, digoxin remains in widespread use.

2 We assessed the pharmacokinetic and pharmacodynamic interaction between oral cicloprolol 50 mg day⁻¹ and oral digoxin 0.25 mg day⁻¹ in 10 healthy male volunteers, using a double-blind, randomised protocol, during three 8 day periods. Digoxin was given alone during the first period to reach steady state; then digoxin was given with cicloprolol or placebo during the second and third periods, according to a cross-over design.

3 No significant adverse effects were observed.

4 The pharmacokinetics of digoxin were not different significantly at the end of the placebo-digoxin and cicloprolol-digoxin periods.

5 A significant increase in minimum heart rate and mean nocturnal heart rate, assessed by 24 h Holter recordings, was observed at the end of the cicloprolol-digoxin period as compared with the placebo-digoxin period (means $\pm$ s. e. mean, 57.1 $\pm$ 3.2 beats min⁻¹ vs 52.2 $\pm$ 3.1 beats min⁻¹, $P < 0.01$; and 65.6 $\pm$ 3.8 beats min⁻¹ vs 59.9 $\pm$ 3.9 beats min⁻¹, $P < 0.01$, respectively).

6 A significant increase in left ventricular ejection fraction and shortening fraction, assessed by echocardiography, was noted at the end of the cicloprolol-digoxin period as compared with the placebo-digoxin period (means $\pm$ s.e. mean, 66.4 $\pm$ 1.4% vs 61.3 $\pm$ 1.2%, $P < 0.05$; and 37.0 $\pm$ 1.1% vs 33.3 $\pm$ 0.9%, $P < 0.05$, respectively).

7 These results demonstrate that cicloprolol does not modify digoxin pharmacokinetics in healthy male volunteers; they also show that the coadministration of the two drugs induces a positive inotropic effect and is well tolerated in these subjects.

Keywords cicloprolol β_1 -adrenoceptor partial agonist digoxin left ventricular function

Introduction

Cicloprolol (SL 75.177-10) is a partial β_1 -adrenoceptor agonist. Its intrinsic sympathomimetic effect, which varies slightly with the experimental model used, is in the order of 30 to 40% that of isoprenaline. Cicloprolol shows a high selective affinity for β_1 -adrenoceptors (Hicks *et al.*, 1987). This partial β -adrenoceptor agonist effect has been confirmed in man, both in healthy volunteers (McCaffrey *et al.*, 1988a), and in patients with coronary artery disease or moderate left ventricular failure (Silke *et al.*, 1988). In addition, owing to its high absolute bioavailability (approximately 90%) coupled with an elimination half-life of 10 h (Thenot *et al.*, 1989), cicloprolol would appear to be suitable for long-term oral therapy.

One of the major indications for partial β_1 -adrenoceptor agonists is in the treatment of moderate left ventricular failure, particularly that of ischaemic origin. In such patients, the adequacy of long-term digitalis therapy has been questioned when sinus rhythm is present (Gheorghiade & Beller, 1983; Moss *et al.*, 1981; Yusuf *et al.*, 1986). Nevertheless, in general practice the use of cardiac glycosides remains widespread for this indication. Therefore, we studied the possible pharmacokinetic and pharmacodynamic consequences of the co-prescription of these two drugs.

The study was performed in healthy volunteers and not in patients with coronary artery disease and impaired left ventricular function since the assessment of the interaction required the prescription of digoxin alone, without any other drug, for too long a period to be ethically acceptable in subjects with severe coronary insufficiency and impaired left ventricular function.

Methods

Subjects

All subjects of the trial were carried out according to the recommendations of the Declaration of Helsinki. The protocol of the study was approved by the Ethics Committee of the Cochin-Port Royal Hospital. All subjects gave written informed consent to participate in the study.

Ten healthy, male Caucasian volunteers were included in the study. Their mean age was 24 years (range, 21–26), mean weight was 69 kg (range, 66–76) and mean height was 1.78 m (range, 1.70–1.86). A full clinical examination, haematological and biochemical tests, 12-lead

electrocardiogram and continuous 24 h Holter monitoring were carried out before the beginning of the study to confirm the absence of any abnormality. High quality echocardiographic images were obtained in all volunteers. The subjects had not received any drug treatment for 15 days preceding the study and did not receive any drug, other than those described in the protocol, throughout the study.

Experimental design

The double-blind, randomised, placebo-controlled, cross-over protocol was divided into three 8 day periods. During the first 8 day period, each subject received a single daily dose of oral 0.25 mg digoxin in order to achieve steady state plasma digoxin concentrations. During the next two 8 day periods, the subjects received, on a double-blind basis and in random order, cicloprolol (single oral 50 mg dose day⁻¹) and placebo, in addition to digoxin (single oral 0.25 mg dose day⁻¹). Thus, five subjects received cicloprolol and five others received placebo during the second period with a cross-over for the third period, without wash-out between the second and third periods. The dosage of digoxin used was that most frequently prescribed in general practice. The cicloprolol dosage corresponded to that which, as shown by available clinical data, produced β -adrenoceptor blockade and partial agonist effects whilst being well tolerated clinically (McCaffrey *et al.*, 1988a; Silke *et al.*, 1988).

Pharmacokinetic study

In order to compare the plasma concentration-time data and pharmacokinetic parameters of digoxin ($t_{\max}$, $C_{\max}$, AUC), 10 ml venous blood samples were collected into heparinized tubes on study days 16 and 24 before digoxin administration, and 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h after the oral dose. The samples were centrifuged, the plasma was frozen immediately and it was stored at -20°C . Plasma digoxin concentrations were measured by radioimmunoassay (gamma coat ^{125}I kit, CA 547, Travenol Laboratories, Maurepas, France). This method is based on competition for antibody binding sites between plasma digoxin and radio-labelled digoxin (Smith *et al.*, 1969). Samples and standards were incubated with radio-labelled digoxin in antibody-coated tubes at 37°C for 1 h. After incubation the content of the tubes was withdrawn and the radioactivity counted

for 2 min in a gamma counter. A calibration curve was prepared from four standard serums containing drug concentrations ranging from 0.5 to 4 ng ml⁻¹. As cross-reactions may occur in this type of assay, tests were carried out on plasma samples spiked with cicloprolol at therapeutic concentrations. The radioimmunoassay of digoxin was not affected by the presence of cicloprolol. The percentage recovery of digoxin was 86% with a precision and reproducibility that was normal for a radioimmunoassay (Smith *et al.*, 1969; Weintraub, 1983).

Pharmacodynamic parameters

A pharmacodynamic interaction between digoxin and cicloprolol was investigated on the basis of the chronotropic and inotropic effects of the two drugs.

Chronotropic effects were assessed by continuous Holter monitoring. A 24 h Holter recording (using two bipolar precordial leads, ELA Medical recorder, analysed with an ANATECH computer) was carried out on days 16 and 24 at the end of cicloprolol-digoxin or placebo-digoxin administration. Maximum, minimum, and mean diurnal and nocturnal heart rates recorded during the two coadministration periods were compared.

Inotropism was studied by echocardiography. In each subject, three echocardiographic examinations were carried out by the same experienced echocardiographer, before the beginning of the study and at the end of each of the two 8 day periods of cicloprolol-digoxin and placebo-digoxin administration. Subjects were only included in the study if, in a position of dorsal decubitus or left lateral decubitus, it was possible to obtain high quality and reproducible images from which the ventricular diameter could be measured with a precision of 1 mm. The echocardiograms were displayed with an ATL (Advanced Technology Laboratories) apparatus, ultramark 8 model, connected to an electro-mechanical scanner composed of two 3 MHz rotating piezoelectric crystals giving a 90 degree angle aperture. The echographic images were taken at the end of expiration. Two separate images were collected for each subject at each of the three echographic examinations to check on the reproducibility of the measurements. For statistical analysis, the mean of the two measurements was used. Measurements of left ventricular end-diastolic and end-systolic diameters were taken from a 1-dimensional image TM, the cross-section of which was selected by 2-dimensional scanning with a technique previously used in this laboratory (Weber

et al., 1983). The interpretation of the tracings was carried out on a blind basis. Measurements of left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) allowed the calculations (Weber *et al.*, 1983) of the left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), as well as the left ventricular shortening fraction (LVSF) and ejection fraction (LVEF):

$$\text{LVSF} = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}}$$

$$\text{LVEF} = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}}$$

Clinical and laboratory data

The subjects were monitored clinically throughout the study; haematological and biochemical tests were carried out at the beginning and the end of the study.

Statistical analysis

The data were subjected to analyses of variance based on the order of administration and drug factors.

Results

All subjects completed the study, no significant adverse clinical events were observed and the final laboratory tests did not reveal any abnormalities.

Pharmacokinetic data

Table 1 shows the pharmacokinetic parameters of digoxin following the last dose of the periods of coadministration with cicloprolol or placebo.

Following coadministration of placebo, the mean peak plasma concentration of digoxin (1.7 ng ml⁻¹) occurred approximately 1 h after the dose, and the mean area under the plasma concentration-time curve between 0 and 24 h (AUC) was 12.8 ng ml⁻¹ h. These values were not significantly different following coadministration of cicloprolol.

Pharmacodynamic data

Holter recordings did not show any significant disturbances, in particular no atrial or ventri-

Table 1 Pharmacokinetic parameters (mean $\pm$ s.e. mean and range) of digoxin following coadministration of placebo and cicloprolol

	Placebo-digoxin	Cicloprolol-digoxin
$t_{\max}$ (h)	1.0 $\pm$ 0.2 (0.5–2)	1.1 $\pm$ 0.3 (0.5–4)
$C_{\max}$ (ng ml ⁻¹)	1.7 $\pm$ 0.2 (1.1–2.7)	1.7 $\pm$ 0.1 (0.9–2.4)
AUC(0,24) (ng ml ⁻¹ h)	12.8 $\pm$ 1.8 (6.4–27)	11.3 $\pm$ 1.3 (4.3–20.1)

Table 2 Results (mean $\pm$ s.e. mean) of Holter recordings and echocardiograms at the end of the placebo-digoxin and cicloprolol-digoxin periods

	Placebo-digoxin	Cicloprolol-digoxin	P
<i>Holter recordings:</i>			
Maximum heart rate	102.7 $\pm$ 5.3	107.0 $\pm$ 5.4	NS
Minimum heart rate	52.2 $\pm$ 3.1	57.1 $\pm$ 3.2	< 0.01
Mean diurnal heart rate	71.6 $\pm$ 3.1	74.9 $\pm$ 4.1	NS
Mean nocturnal heart rate	59.9 $\pm$ 3.9	65.6 $\pm$ 3.8	< 0.01
<i>Echocardiograms:</i>			
LVEDD	5.0 $\pm$ 0.1	5.0 $\pm$ 0.1	NS
LVESD	3.3 $\pm$ 0.1	3.2 $\pm$ 0.1	NS
LVEDV	120.2 $\pm$ 6.0	120.2 $\pm$ 6.0	NS
LVESV	45.5 $\pm$ 2.7	40.4 $\pm$ 2.8	NS
LVEF	61.3 $\pm$ 1.2	66.4 $\pm$ 1.4	< 0.05
LVSF	33.3 $\pm$ 0.9	37.0 $\pm$ 1.1	< 0.05

Heart rates (beats min⁻¹)

LVEDD: left ventricular end-diastolic diameter (cm)

LVESD: left ventricular end-systolic diameter (cm)

LVEDV: left ventricular end-diastolic volume (cm³)LVESV: left ventricular end-systolic volume (cm³)

LVEF: left ventricular ejection fraction (%)

LVSF: left ventricular shortening fraction (%)

NS: not significant ($P > 0.05$)

cular hyperexcitability, and no atrioventricular conduction abnormalities. For technical reasons (electrodes moved, defective mechanism), good quality tracings were not obtained during the night of both periods in one subject and during the night of the placebo-digoxin period in another subject. A significant increase in minimum heart rate and mean nocturnal heart rate was observed at the end of the cicloprolol-digoxin period as compared with the placebo-digoxin period (Table 2). No significant differences between these two periods were observed for the maximum heart rate and the mean diurnal heart rate.

Echocardiographic data (Table 2) did not show any significant differences in left ventricular

diameter and volume values observed before the study (mean $\pm$ s.e. mean, LVEDD: 5.0 $\pm$ 0.1 cm; LVESD: 3.5 $\pm$ 0.2 cm; LVEDV: 121.5 $\pm$ 6.0 cm³; LVESV: 47.4 $\pm$ 3.5 cm³) and those obtained at the end of the placebo-digoxin and cicloprolol-digoxin periods. However, a significant increase in left ventricular ejection fraction and shortening fraction was observed at the end of the cicloprolol-digoxin period as compared with both the placebo-digoxin period and the values noted before the study (mean $\pm$ s.e. mean, LVEF 61.3 $\pm$ 1.5%, $P < 0.05$; LVSF: 33.3 $\pm$ 1.0%, $P < 0.05$). There were no significant differences between the placebo-digoxin period and the baseline values for the left ventricular ejection fraction and shortening fraction.

Discussion

This study in 10 healthy male Caucasian volunteers, who received doses of digoxin and cicloprolol of the same order of magnitude as those used, or which could be used, therapeutically, demonstrated that cicloprolol did not modify digoxin pharmacokinetics, and that the coadministration of the two drugs induced a significant positive inotropic effect and were well tolerated.

The absence of significant modification of the pharmacokinetic parameters of digoxin following coadministration of cicloprolol in healthy volunteers may be extrapolated to patients with coronary insufficiency without signs of decompensated heart failure. In contrast, these results in healthy volunteers do not rule out the possibility of an interaction under conditions in which digoxin pharmacokinetics would be modified such as oedema of decompensated heart failure, organic or functional renal failure, or the concomitant prescription of drugs which modify digoxin pharmacokinetics (some antiarrhythmics, in particular quinidines, and calcium antagonists) (Doherty & Perkins, 1962; Weintraub, 1983).

The absence of any rhythm or conduction disturbances following digoxin-cicloprolol coadministration in healthy volunteers does not obviate the need for careful re-assessment of this combination in patients in whom the ischaemic myocardium is potentially much more sensitive to any negative dromotropic and arrhythmogenic effects. Currently available studies indicate that the partial β_1 -adrenoceptor agonist effect of cicloprolol is manifested by a moderate increase in resting heart rate (Rigaud *et al.*, 1988). In the present study, concomitant administration of digoxin did not appear to modify the positive chronotropic effect of cicloprolol in resting subjects.

This study does not distinguish whether the observed inotropic effect was due to cicloprolol alone or to the combination of digoxin and

cicloprolol. However, the absence of a significant difference in left ventricular contractility between the baseline and placebo-digoxin period echocardiograms appears to indicate that most, if not all, of the inotropic effect might be attributed to cicloprolol. These results confirm data from previous clinical (McCaffrey *et al.*, 1988a), haemodynamic (Rigaud *et al.*, 1988), and isotopic (Silke *et al.*, 1988; Weber *et al.*, 1985) studies, which showed a positive inotropic effect of cicloprolol on both the healthy and the ischaemic myocardium. These effects of cicloprolol are comparable with those observed after the oral administration of xamoterol, another β_1 -adrenoceptor partial agonist, which in healthy volunteers increases sleeping heart rate (McCaffrey *et al.*, 1988b) and has a positive inotropic effect (Kullmer *et al.*, 1988).

Partial β_1 -adrenoceptor agonists are able to produce, in patients with coronary artery disease and impaired left ventricular function, both β -adrenoceptor blockade, limiting the myocardial oxygen consumption of excessively raised sympathetic tone (effort, stress), and, due to their intrinsic sympathomimetic activity, a significant positive inotropic effect improving left ventricular function. Thus, partial beta-agonists appear particularly appropriate in the treatment of patients with coronary insufficiency with markedly impaired left ventricular function, who have a poor spontaneous prognosis and in whom the use of β -adrenoceptor blockers (devoid of intrinsic sympathomimetic effect) is often impossible owing to adverse haemodynamic effects. Any effect of partial β_1 -adrenoceptor agonists on the prognosis of this type of patients remains to be established.

Further studies are indicated to assess the tolerance and pharmacodynamic effects of the concomitant administration of cicloprolol and digoxin in patients with poor left ventricular function.

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