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Effect of urapidil on steady-state serum digoxin concentration in healthy subjects

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Summary. In an open, randomized, two-period change-over study the effect of urapidil, an antihypertensive agent, on steady-state serum digoxin levels was investgated in 12 healthy male volunteers. The subjects were given digoxin 0.25 mg once daily for 4 days to produce a steady-state digoxin level in serum. At the end of that time the subjects received either digoxin monotherapy or digoxin and concomitant treatment with urapidil 60 mg b.d. for a further 4 days. Subsequently the treatments were changed over.

The absorption characteristics C_{max} and t_{max} of digoxin were not altered by concomitant urapidil treatment. The geometric mean and nonparametric 95% confidence limits of digoxin relative bioavailability were 97% (93%-103%).

Therefore, concomitant administration of urapidil with digoxin treatments did not appear to alter the rate and extent of absorption of the glycoside.

Key words: urapidil, digoxin; blood drug level, pharmacokinetics, drug absorption/-interaction

Hypertensive patients who also have congestive heart failure may be treated by concomitant administration of digoxin and urapidil, a postsynaptic α_1-adrenoceptor blocker [1] and a central serotonergic receptor agonist [2].

As it is important to know whether concomitant administration of digoxin and urapidil requires adjustment of the dose of digitalis, the pharmacokinetics of digoxin with and without concomitant urapidil treatment have been investigated in healthy volunteers under strictly controlled conditions.

Materials and methods

An open, randomized, cross-over study, comprising 2 treatment periods each of 4 days, and 4 days of pretreatment with digoxin, was performed in 12 healthy male volunteers, aged 20 to 44 years (median, 31 years), and weighing 62 to 84 kg (mean 71.6 kg). Prior to the study physical and laboratory examinations as well as an ECG were performed. The study protocol was approved by an Institutional Review Board and each volunteer gave written informed consent before his participation.

Medication was administered in the morning at 08.00 h and in the evening at 20.00 h. Drug intake of medication with 200 ml water was supervised.

Standardized meals were served daily at 07.00 h, 12.00 h, and 18.00 h. Alcohol, as well as food and beverages containing xanthines, were not permitted.

At the end of the 4-day digoxin pretreatment (1st day 0.25 mg b.d., Days 2 to 4 0.25 mg once daily) the subjects were randomly allocated to receive either digoxin monotherapy (0.25 mg once daily) or digoxin 0.25 mg once daily and urapidil 60 mg b.d. for 4 days. At the end of that period (Day 9) the treatments were changed over.

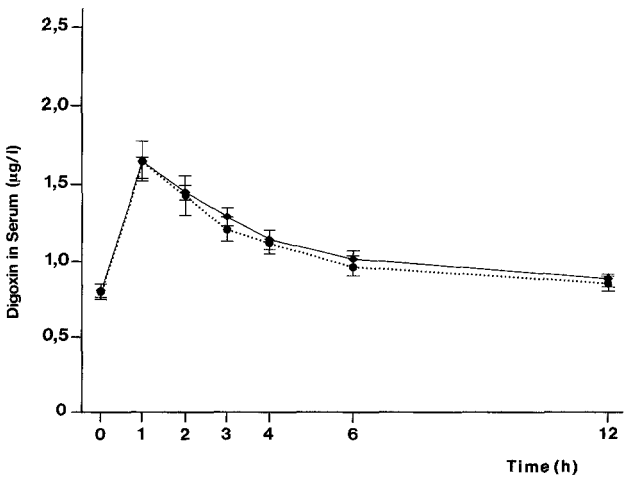

Fig. 1. Concentration/time profiles (mean (SEM)) of serum digoxin with (...) and without (—) concomitant urapidil treatment

Blood samples for the determination of digoxin were collected on Day 5, before the morning dose, and on Days 8 and 12 for assay of serum digoxin and urapidil. They were taken 0, 1, 2, 3, 4, 6, 12 and 24 h (digoxin only) after each morning dose. On Days 8 and 12 the subjects received urapidil 60 mg only in the morning.

Blood pressure and pulse rate were measured once supine and standing before blood samples were taken..

Serum digoxin was measured by radio-immuno-assay (RIA) and urapidil by HPLC [3]. Serum digoxin was analyzed at the Labor für Pharmakokinetik und Biopharmazie (Munich, FRG) using a commercially available RIA Kit (Diagnostic Products Corporation, USA), modified by using twice the amount of serum and a 24-h incubation. A double antibody system was used as the separation step. The coefficient of variation for 50 pg/100 µl serum ($n=20$) was 4.6% and for 200 pg/100 µl serum it was 6.2%.

Parameters are shown as mean (SEM), as well as median, minimum and maximum. The effects of the two treatments were compared by the two-sided Wilcoxon-Pratt test [4]. In the case of ratio analysis, geometric mean and nonparametric 95%-confidence limits according to Tukey are given as point and interval estimators [5].

The maximum serum concentration C_{max} and its time of occurrence, t_{max}, were determined for digoxin serum both during monotherapy and the concomitant treatment period. Areas under digoxin concentration/time curves (AUC) were calculated by the trapezoidal rule for 1 dosage interval (i.e. 24 h). Bioavailability in each subject was determined by the ratio of the AUCs of digoxin treatment with and without urapidil.

Results

There were no differences in digoxin concentration/time profiles in subjects receiving digoxin monotherapy or digoxin/urapidil treatment (Fig. 1). The maximum serum digoxin C_{max} 1.71 (0.10) µg/l (mean (SEM)) during digoxin monotherapy was found 1 h (median) after the morning dose; corresponding values for concomitant treatment with urapidil were 1.74 (0.13) µg/l and 1 h (NS).

Comparing individual results in each volunteer, the relative bioavailability of digoxin ranged between 72% and 114%; the geometric mean and nonparametric 95%-confidence limits of relative bioavailability were 97% (93%–103%). Considering 80%–120% to be the bioequivalence range [6], coadministration of urapidil with digoxin treatment had no influence on the bioavailability of digoxin.

Serum urapidil levels were within the range found in previous trials [7].

Blood pressure and pulse rate, both supine and standing, showed normal daily variation with no difference between digoxin monotherapy and digoxin/urapidil treatment. Taking the urapidil did not lower the blood pressure more than expected.

Two subjects complained of side effects (headache and slight palpitations). Headache was most probably not drug related. Palpitations were attributed to digoxin medication.

The maximum serum concentration C_{max} of digoxin was neither decreased nor increased on concomitant treatment with urapidil as compared to digoxin monotherapy. The time of the peak serum concentrations (t_{max}) was not prolonged or shortened by the combined treatment. Therefore, urapidil does not appear to alter the rate of absorption of digoxin.

The extent of digoxin absorption, which is described by the AUCs, too, was not influenced by urapidil. The geometric mean (97%) and nonparametric 95%-confidence limits (93%–103%) were within the bioequivalence range of 80%–120%.

Concomitant treatment with urapidil of patients adjusted to digoxin therapy, from a pharmacokinetic point of view, can be undertaken without hesitation.

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