Pharmacokinetics of Slow-Release Diltiazem and Its Effect on Atrioventricular Conduction in Healthy Volunteers

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Summary. The pharmacokinetics and effect of a slow-release and a conventional diltiazem tablet on atrioventricular conduction were compared in a randomized cross-over study after a single dose and at steady state in 12 healthy volunteers.

The time to peak concentration was significantly delayed after the slow-release as compared to the conventional tablet, both after a single dose (2.7 vs. 0.9 h) and at steady-state (1.9 vs. 0.9 h). The peak concentration was also significantly reduced. There was no marked loss in bioavailability with the slow-release formulation. The maximal fluctuations in serum diltiazem at steady-state for the slow-release tablet were markedly less than after the conventional tablet (62 vs 87%). The PQ-interval was longer after the conventional tablet as compared to the slow-release tablet (both in doses of 120 mg) after a single dose (187 vs 163 ms) and at steady-state (197 vs 174 ms). The maximal prolongation was seen 1 h after intake of the drug. Heart rate was decreased only by 6-9 beats/min, irrespective of the dose. Slow-release diltiazem appears to have many advantages over a conventional tablet.

Key words. Diltiazem; slow-release tablet, pharmacokinetics, atrioventricular conduction, healthy volunteers

Diltiazem is a benzothiazepine derivative with coronary and other smooth muscle calcium channel blocking activity. It is a potent vasodilator useful in the treatment of angina pectoris, arterial hypertension, pulmonary hypertension, hypertrophic cardiomyopathies and probably supraventricular tachyarhythmias [3].

The pharmacokinetics of diltiazem has been extensively studied [3]. Diltiazem has relatively short half-life of about 4-5 h and is usually administered three or four times daily. Attempts have been made to develop slow-release formulations with an extended clinical effect.

There is some controversy about the effect of diltiazem on atrioventricular conduction. In some studies diltiazem has not changed the PQ-interval [1, 4, 13], but prolongation has also been reported [5, 11, 12].

The aim of the present study was to investigate the pharmacokinetics of a new slow-release diltiazem tablet as compared to a conventional tablet, and to examine their effect on atrioventricular (AV) conduction in healthy volunteers. The studies were performed both after a single dose of the drugs and in the steady-state condition.

Subjects and Methods

Twelve healthy volunteers, 8 men and 4 women, aged 21–26 years, weighing 59–90 kg, participated in the study. A physical examination and haematological, liver and kidney function tests were performed before the study. The purpose of the study was explained to the subjects and informed consent was obtained. The study was accepted by the internal Ethical Committee.

The drugs studied were 1) a conventional 60 mg and 2) a slow-release 120 mg diltiazem tablet with a break score (Orion Pharmaceutica, Espoo, Finland). The doses used were 120 mg b.i.d. for the conventional and 120 mg and 180 mg (1½ tablets) b.i.d. for the slow-release tablet. The study followed a cross-over randomized design.

After an overnight fast, at 8 a.m. on the first day of the study each subject was given a single dose with 100 ml water. Eating was allowed 4 h later. From the second morning onwards, the dose was administered twice daily (dose interval 12 h) for 4 days. The last dose was taken at 8 a.m. on the 6th day. It was followed by a two-week wash-out period, after which the next study period was started.

Blood samples for diltiazem determination were taken on Days 1, 5 and 6 before the morning dose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after it. The sera were separated by centrifugation and kept frozen at -20°C until analysed.
The determination of diltiazem in serum after solvent extraction was performed by capillary gas chromatography using a nitrogen sensitive detector. The chromatographic system consisted of an HP 5730 A instrument and an HP 3388 A integrator (Hewlett-Packard, Avondale, PA, USA). The fused silica capillary column OV-1701 (bonded phase, 0.25 μm, 6 m × 0.32 mm, i.d., Orion Analytica, Espoo, Finland) was held at 255 °C. Injector and detector temperatures were 300 °C. Helium flow as carrier gas was 2 ml/min. Injection was performed in the isothermal splitless mode with a 7-s delay time using an Hewlett-Packard automatic sampler 7672 A. The retention times were 2.1 min and 3.5 min for diltiazem and internal standard thiethylperazine, respectively.

Serum samples were prepared by adding 0.1 N NaOH 300 μl to 1.0 ml serum. The sample was shaken for 5 min with 4.0 ml distilled diethyl ether. After centrifugation 3.0 ml solvent was evaporated to dryness in the gentle stream of nitrogen at 35 °C. The residue was dissolved in 50 μl ethanol-tetradecane (2:98 v/v) containing 100 ng internal standard thiethylperazine. An 0.5 μl aliquot was analyzed. Standard samples were prepared by adding diltiazem hydrochloride in 50 μl water to 1.0 ml serum mixing and then treating them in the same way as clinical samples.

Diltiazem was quantitated by comparing peak height ratios of diltiazem and the internal standard to a linear regression calibration line, which was constructed daily. A typical correlation coefficient in the range 5-750 ng/ml was 0.999.

The lowest detectable amount of diltiazem was 7 pg at a signal to noise ratio of 3. The quantitation limit was 2 ng/ml serum. Precision, studied by assay of spiked serum samples, was 5% (c.v., n = 6) and 3% (c.v., n = 6) at concentrations of 25 ng/ml and 100 ng/ml, respectively. Day-to-day precision was 6% (c.v., n = 5) at 40–150 ng/ml. Recovery was studied by comparing spiked serum samples with samples to which diltiazem in diethyl ether was added after the final evaporation step. At 25 and 100 ng/ml recovery was 81% ± 4% (± SD, n = 6) and 87% ± 3% (± SD, n = 6), respectively. The analysis was specific for diltiazem. No interfering peaks were observed in blank serum at the retention times of diltiazem or the internal standard. The desacetyl metabolite of diltiazem did not disturb the quantitation of diltiazem.

Heart rate (HR) and PQ-interval were measured before and 1 and 3 h after intake of the first dose, and 1 and 3 h after the morning dose on the 6th day of medication. HR and PQ-interval were measured from the ECG (Mingograph 62) recorded in the supine position, after a 10 min rest. The paper speed was 50 mm/s, and the PQ-interval was measured with an accuracy of 10 ms.

Student's t-test for paired values (for Cmax, Cmin, AUC) and Wilcoxon's rank test (for tmax) were applied to the pharmacokinetic data. Friedman's analysis of variance was used for comparison of ECG data, followed, if statistical significance was found, by the paired test of Colquhoun. The maximal fluctuations in serum concentrations were calculated as percentages of the maximal serum concentrations

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\frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{max}}} \times 100.
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The retard quotient was calculated according to Meier et al. [8]. The pharmacokinetic parameters were calculated from the measured values.

**Results**

The mean serum diltiazem concentrations on the 1st and 6th days are graphically illustrated in Fig.1. The steady-state level was reached by the 5th day, since there were no significant differences in pharmacokinetics between the 5th and 6th days. There was a 4.2-fold interindividual variation in peak serum concentrations on the 6th day after treatment with the conventional tablet. After the 120 mg and 180 mg slow-release treatments, the maximal variations were 3.4-fold for both strengths.

The mean values of the main pharmacokinetic parameters are shown in Table 1. They have been derived from the serum concentrations after the first dose and after the morning dose on the 6th day. The peak concentration (Cmax) was significantly lower and delayed after the slow-release as compared to the conventional tablet. The Cmin values were significantly higher after the slow-release tablet as compared to the conventional tablet.

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Fig. 1. Serum diltiazem concentration after a single dose (Day 1) and at steady-state (Day 6) after conventional and slow-release diltiazem tablets in 12 healthy volunteers.