Pharmacokinetics of pirmenol in young and elderly subjects

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Summary. The steady state pharmacokinetics of pirmenol was compared in twelve healthy young (aged 18 to 45 y) and 11 elderly subjects (over 65 y) subjects given pirmenol HCl 100 mg every 12 h for a total of 14 doses. In addition, the single-dose pharmacokinetics of pirmenol was determined following a 100 mg oral dose in the young subject group for comparison with the results of repeated administration.

In the young subjects, the mean single-dose and steady-state CLR of pirmenol were similar; however, Ae was 29% higher and CL/f was 22% lower at steady state than after the single dose. Steady-state (fourteenth dose) Cₘₘₐₓ, Cₘₚₘₚₑₚₚₑₚₑ, tₚₖₚₑₚₑ, Ae, CL/f, CLR and V values were similar in the young and elderly subjects.

Based on pharmacokinetic considerations, the dosage of pirmenol is unlikely to differ in young and elderly subjects.

Key words: Pirmenol; pharmacokinetics, elderly subjects, age effect, adverse effect

Pirmenol, (cis-(+)-3-(2,6-dimethyl-l-piperidinyl)propyl]-[phenyl-2-pyridinemethanol] is a new Class 1A antiarrhythmic agent. It has been shown to reduce premature ventricular complexes in patients [de Buitleir et al. 1988] and it also has demonstrated utility in the treatment of ventricular tachycardia [Easley et al. 1986; Ester et al. 1987]. Since pirmenol may be administered to elderly patients, the steady-state pharmacokinetics of pirmenol has been investigated in subjects over 65 y of age and the results compared to those in subjects between the ages of 18 and 45 y. In addition, since pirmenol was administered as a single dose in most previous pharmacokinetic studies, both single-dose and steady-state pharmacokinetics were investigated in the young subjects.

Subjects and methods

Subject selection

Twenty-three healthy adult volunteers, as determined by history, physical examination, and clinical laboratory profiles, gave informed consent and participated in the study. Twelve young subjects had a mean (range) age of 25 (19–38) y, a mean (range) weight of 65.8 (49–95) kg, and a mean (range) height of 170 (153–186) cm, and 11 elderly subjects had a mean (range) age of 71 (67–74) y, a mean (range) weight of 70.4 (51–93) kg, and a mean (range) height of 175 (158–187) cm. Eleven of the volunteers were female and six were of reproductive potential and used a reliable method of contraception during the study. Ethical approval for the study was granted by the Otago Area Health Board's Ethics Committee.

Study design

All subjects received 100 mg pirmenol hydrochloride every 12 h for a total of 14 doses. Young subjects also received a single 100 mg dose of pirmenol hydrochloride 1 week prior to the multiple-dose phase. Clinical safety monitoring was performed throughout the study.

Specimen collection

Venous blood samples of 10 ml were collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 h following administration of the single dose to young subjects. During multiple-dose pirmenol administration, blood samples were collected daily prior to the morning dose. Following the final (14th) dose of pirmenol, blood samples were collected immediately prior to and after 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 h from both young and elderly subjects. Blood was collected into heparinised tubes, centrifuged, and the plasma stored at −20°C until analysed for the pirmenol concentration.

All urine passed by the young subjects during the 24-h period following the single dose and by young and elderly subjects during the 12-h period following the final dose of the multiple-dose phase was collected. Volumes were recorded and samples were stored at −20°C until assayed for pirmenol concentration.

Assay procedures

Pirmenol concentrations in plasma and urine were measured by reverse phase HPLC. In summary, plasma samples were made basic with 1 M NaOH and extracted with tert-butylmethylether. The organic layer was evaporated to dryness and the residue dissolved in 0.2% phosphoric acid. Separation was done on a reversed-phase Spherisorb C8 column (10 cm x 2.1 mm id) with a mobile phase consisting of acetonitrile:water (7.5:92.5) containing 0.1% phosphoric acid and 4 mM dibutylamine phosphate, and detection was by ultraviolet absorbance at 260 nm. Quantification employed the peak-
Results

Clinical

Eleven young subjects and ten elderly subjects completed the trial. Two subjects withdrew due to adverse events. One young subject had a mildly elevated eosinophil count at screening, which increased further after the first two doses of pirmenol in the multiple dose phase of the study. The subject was withdrawn from the trial and the eosinophil count subsequently returned to its pretreatment level. One elderly subject experienced mild bradycardia 2 days after commencement on multiple dose pirmenol, which resolved after discontinuation of the drug. Three elderly subjects experienced mild nausea and four subjects complained of a dry mouth after administration of multiple doses of pirmenol.

There was a small increase in serum creatinine concentrations in both young and elderly subjects at the end of the study when compared to the pre-test values ($P < 0.05$ Wilcoxon rank sum test). Re-analysis of the other samples obtained during the study showed that the mean serum creatinine concentration initially increased significantly, although remaining within the normal range, and remained elevated for several days before declining in the latter days of the study.

Pharmacokinetics

It was not possible to measure pirmenol in plasma from one elderly subject due to an interfering peak in the chromatographic assay which could not be resolved. Questioning of the subject and subsequent analysis revealed that the compound was quinine taken intermittently for cramps. Pharmacokinetic data are therefore presented for the 11 young and 9 elderly subjects for whom all assays were completed.

Mean plasma pirmenol concentration-time profiles for the young and elderly subjects after the last dose of multiple dosing were very similar and are shown in Fig. 1. The mean plasma concentration-time profile in the single-dose study in young subjects is also shown. Pharmacokinetic parameters following administration of single doses to the young subjects and multiple doses to young and elderly subjects are shown in Table 1. There were no statistically significant differences in multiple-dose pharmacokinetic parameters between the young and elderly subjects. The only significant difference was in the AUC in young subjects after single and multiple doses of pirmenol ($P < 0.05$, Wilcoxon rank sum test).

Discussion

Pirmenol is a new antiarrhythmic drug, which is being evaluated for the treatment of ventricular arrhythmias and ventricular tachycardia. Pirmenol is extensively metabolized, although more than 23% of an administered dose is excreted unchanged in urine [Lee et al. 1983]. Thus, age might alter the pharmacokinetics of pirmenol through