Quinidine does not affect the renal clearance of moxonidine

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Aims To test the hypothesis that the renal clearance of moxonidine decreases when dosed with quinidine.

Methods A randomized, two-period study was conducted with six healthy, male subjects orally dosed with either 0.2 mg moxonidine alone or 1 h after 400 mg quinidine sulphate. Pharmacokinetic parameters were calculated using a noncompartmental analysis method.

Results When coadministered, quinidine significantly increased moxonidine AUC and $t_{1/2}$ by 11% and 15%, respectively, and decreased CL/F by 10% compared with the control dosing. CL_R and Ae_{ur} were not significantly different. Clinically, both treatments were well tolerated.

Conclusions Quinidine does not affect the renal clearance of moxonidine. The decrease in apparent total clearance of moxonidine with quinidine coadministration was possibly due to metabolic inhibition, though not likely to be clinically significant.

Keywords: moxonidine, pharmacokinetics, quinidine, renal

Introduction

Moxonidine is a well-tolerated and effective antihypertensive agent, acting on central nervous system imidazoline receptors to decrease sympathetic tone. Due to its minimal action on α_2 -adrenoceptors, moxonidine causes less sedation compared with other centrally acting antihypertensive agents [1].

Taken orally, moxonidine is well absorbed, reaching a peak plasma concentration by about 1 h with an elimination half-life of about 2 h. Approximately 60% of the drug is excreted unchanged in the urine [2]. As the majority of the drug is cleared renally, and the clearance is substantially higher than the glomerular filtration rate [3], it is reasonable to assume that moxonidine is subject to active renal secretion. Currently, the exact mechanism is not known. However, moxonidine pharmacokinetics were not altered with coadministration of glibenclamide [4]. An *in vitro* study has shown that glibenclamide is both

a substrate and inhibitor of P-glycoprotein (PGP) [5], which may indicate that active renal secretion of moxonidine is not likely through a PGP pathway.

Although some compounds are transported via both the PGP and the organic cation secretion pathways, it has been shown that certain compounds, such as tetraethylammonium, interact selectively with the organic cation transport system [6]. Therefore it remains plausible that moxonidine is actively secreted through an organic cation secretion pathway in the renal proximal tubule. Quinidine sulphate, a potent inhibitor of organic cation secretion, was coadministered with moxonidine to determine whether the pharmacokinetics of moxonidine are altered in the presence of quinidine.

Methods

Subjects and clinical protocol

Six healthy, male, Oriental subjects aged between 23 and 24 years, with mean $\pm$ s.d. weight of 67.8 ± 5.4 kg gave written informed consent to participate in this study. The study was approved by the Research and Ethics Committee of the National University of Singapore and performed in accordance with the Declaration of Helsinki.

This was an open label, randomized, two-period, crossover study. Subjects fasted for 8 h prior to dosing and for 4 h subsequently. Subjects voided their bladder

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immediately prior to dosing. Depending on the random dosing sequence, subjects received oral 0.2 mg moxonidine alone or 0.2 mg moxonidine 1 h after 400 mg quinidine. There was a minimum washout interval of 3 days before the second period. For both treatment periods, 7 ml venous blood was collected at time 0 (pre-moxonidine dose) and then at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 h post-moxonidine dose. An additional pre-quinidine dosing sample was also taken for that period. Urine voided over 48 h after moxonidine dosing was collected.

Drug assay

Blood samples were centrifuged to obtain plasma, and kept at approximately -70°C until time of analysis. Moxonidine concentrations were analysed using an atmospheric pressure chemical ionization/LC/MS/MS system validated within the range of 0.05–8.00 and 0.25–16.0 ng ml $^{-1}$ for the plasma and urine assays, respectively. The calibration curve correlation coefficients were no less than 0.9955 using (^{13}C) $_3$ -moxonidine as an internal standard. Quinidine plasma concentrations were assayed using a h.p.l.c. technique with fluorescence detection based on a previously described method [7]. Using campothecin as an internal standard, the standard curve was validated over the range of 50–5000 ng ml $^{-1}$, with a correlation coefficient of 0.9991. The intra- and interday variability determined over the validated concentration range for all assays was less than 12% (Oneida Research Services Inc., Whiteboro, NY, USA).

Pharmacokinetic analysis

Data were analysed using a noncompartmental pharmacokinetic approach (WinNonlin Professional Network Edition ver 1.5), using actual sampling times. The parameters calculated were: peak concentration (C_{max}), time to reach C_{max} (t_{max}), apparent clearance (CL/F), renal clearance (CL_{R}), nonrenal clearance (CL_{NR}), total amount excreted in the urine (Ae_{ur}), half-life ($t_{1/2}$), area under the plasma concentration-time curve from dosing to time to the last quantifiable concentration ($\text{AUC}(0,t)$), and with extrapolation to infinity (AUC) using the log-linear trapezoidal rule.

Statistical analysis

Assuming intrasubject coefficient of variation (CV) of 15%, six subjects provides 80% power to detect a 28% decrease in mean moxonidine CL_{R} at a 0.05 alpha level. The pharmacokinetic parameters were natural log-transformed and statistically tested using an analysis of variance model. The least squares (LS) means, which are

the expected value of the treatment means when the data are fitted with an analysis of variance model, and the 95% confidence intervals of the mean differences were calculated. A statistically significant difference was inferred when the 95% confidence interval of the geometric LS mean ratio did not include one [8].

Results

Both treatments were well tolerated, with all subjects completing the study. From the urine assay data, subject 4 appeared to excrete more moxonidine than he was dosed when receiving the moxonidine with quinidine treatment, resulting in a higher moxonidine renal clearance compared with the total clearance. No explanation could be given, and the statistical analysis of renal clearance was performed including and excluding these data.

All subjects received similar exposure to quinidine, with a geometric mean (CV%) quinidine AUC of 17028 ng ml $^{-1}$ h (9.09%), and reaching a mean peak plasma concentration of 1520 ng ml $^{-1}$ (6.48%) at a median time of 1.84 h (range 1.67–05.00 h).

Figure 1 illustrates the arithmetic mean $\pm$ s.e. mean concentration-time profiles of moxonidine alone or in combination with quinidine. For the combined dosing, subject 2 appeared to have a degree of lag in t_{max} . The calculated pharmacokinetic parameters with statistical analysis are summarized in Table 1. The geometric LS mean moxonidine C_{max} after administration of moxonidine treatment and after combined treatment was 1.32 ng ml $^{-1}$ and 1.36 ng ml $^{-1}$, respectively, with intra-subject variability of 9.0%. The intrasubject variability for all pharmacokinetic parameters was 18% or less, with the exception of CL_{NR} (42.6%).

Figure 1 Plasma moxonidine concentrations alone (●) and in combination (□) with quinidine. Results are arithmetic mean $\pm$ s.e. mean, $n = 6$. Data at 10 h moxonidine alone treatment, $n = 3$.

Table 1 Geometric LS means with intrasubject CV% and statistical analysis of moxonidine pharmacokinetic parameters.

Parameter	n	Geometric LS means		Intrasubject CV%	Ratio between LS means (B/A)	95% CI on ratio Lower, Upper
		Treatment A	Treatment B			
AUC (ng ml ⁻¹ h)	6	4.27	4.74	3.7	1.11	1.05, 1.18
AUC(0,t) (ng ml ⁻¹ h)	6	4.01	4.50	5.0	1.12	1.03, 1.22
C _{max} (ng ml ⁻¹)	6	1.32	1.36	9.0	1.03	0.89, 1.19
t _{1/2} (h)	6	1.98	2.27	7.9	1.15	1.01, 1.30
CL _R (l h ⁻¹)	6	34.2	35.2	16.0	1.03	0.80, 1.33
CL _R (l h ⁻¹) ^a	5	31.1	32.7	18.0	1.05	0.73, 1.52
CL _{NR} (l h ⁻¹) ^a	5	11.9	8.59	42.6	0.72	0.38, 1.38
CL/F (l h ⁻¹)	6	46.8	42.2	3.6	0.90	0.85, 0.96
Ae _{ur} (μg)	6	146	167	16.5	1.14	0.88, 1.48
t _{max} (h) ^b	6	0.834 (0.33–1.00)	0.667 (0.33–2.00)	NA	NA	NA

Treatment A = moxonidine (0.2 mg), Treatment B = moxonidine (0.2 mg) and quinidine sulphate (400 mg).

^aAnalysis performed excluding subject 4 (Treatment A and B).

^bMedian (minimum–maximum).

Since the 95% confidence intervals of the ratio for C_{max} and CL_R included 1, no significant difference between the two treatments was inferred for these parameters. Analysis of renal clearance did not show statistical significance regardless of whether subject 4 data were included or excluded. Furthermore, the 90% confidence interval of the renal clearance ratio including all subjects was 0.85–1.25, which is within the 0.80–1.25 limits established for bioequivalence (e.g. U.S. Food and Drug Administration). The 90% confidence interval excluding subject 4 was 0.80–1.38. Moxonidine recovery in the urine when given alone or in the presence of quinidine was similar (73% and 79%, respectively). However, a statistically significant 11% and 15% increase in AUC and t_{1/2}, respectively, and a 10% decrease in apparent clearance was observed when moxonidine was coadministered with quinidine.

Discussion

A single 400 mg dose of quinidine did not significantly affect the renal clearance of moxonidine. Furthermore, the 90% confidence interval of the renal clearance ratio was within the range to satisfy bioequivalence, indicating no difference in renal clearance between the two treatments. A statistically significant increase in AUC and t_{1/2} (11% and 15%, respectively) and a 10% decrease in CL/F of moxonidine was observed with quinidine coadministration. The observed moxonidine pharmacokinetic results in this study were consistent with the published literature [1].

This study provided further evidence that moxonidine is not actively secreted via a PGP pathway. Although sharing similarities with the PGP transporter, organic

cation secretion may selectively interact with moxonidine, and was therefore examined in this study. The dose of the organic cation secretion inhibitor, quinidine, was chosen to give over a 600 fold molar excess over the substrate. Assuming multiple organic cation transport systems are not involved, the results of this study indicate that active renal secretion of moxonidine is not significantly affected by the inhibition of the organic cation transport system.

The AUC and t_{1/2} was significantly higher and the total apparent clearance significantly lower for the moxonidine with quinidine treatment, compared to the dosing of moxonidine alone. However, the renal clearance and the total amount of moxonidine excreted in the urine were similar between the treatments. Therefore the increase in AUC of moxonidine in the presence of quinidine is due to a decrease in the non-renal portion of the total apparent clearance. Although the difference in nonrenal clearance was not statistically significant due to high variability and the low number of subjects, the mean value was reduced by 28% with the combined dosing. This finding could be due to a decrease in systemic moxonidine metabolism when coadministered with quinidine, an inhibitor of CYP2D6. A study has shown that moxonidine is extensively metabolized in rats [9]. In addition, although moxonidine is mainly excreted unchanged in humans, at least seven metabolites were identified in the urine samples, which accounted for approximately 20% of the total radioactivity dose after oral administration of radiolabelled moxonidine to healthy subjects (manuscript in preparation). Although the P450 isozyme(s) responsible for the metabolism of moxonidine has not been determined, moxonidine was found to be a competitive inhibitor for the metabolism

of bufuralol (a CYP2D6 substrate) with an apparent inhibition constant value of 89 μM (unpublished data). Therefore, inhibitory effect of quinidine on CYP2D6 could decrease moxonidine clearance if moxonidine is also a substrate of CYP2D6.

The differences in the pharmacokinetic parameters between the two treatments were not considered clinically significant since they were bioequivalent. That is, the 95% confidence interval, and hence the 90% confidence interval of both AUC and C_{max} were within the 0.80–1.25 limits traditionally used for bioequivalence.

When coadministered, quinidine does not affect the renal clearance of moxonidine, indicating that the renal organic cation transport system inhibited by quinidine does not have a major role in the elimination of moxonidine. The observed pharmacokinetic differences in moxonidine were not considered to be clinically significant.

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