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Effect of itraconazole on the pharmacokinetics of celecoxib in healthy human volunteers

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Celecoxib is a non-steroidal anti-inflammatory agent indicated for osteoarthritis and rheumatoid arthritis. The mechanism of action involves the inhibition of cyclo-oxygenase-2 (COX-2) and in turn, inhibition of prostaglandin synthesis [1]. It is metabolized predominantly by the cytochrome P450 isoenzyme 2C9 (CYP2C9) [2], resulting in a possibility of *in vivo* drug interaction [3]. Itraconazole is a synthetic triazole antifungal agent. Anti fungal agents of azole classes are inhibitors of human cytochrome P450 isoforms including CYP2C9 [4, 5]. Co-administration of CYP2C9 substrate drugs with azole derivatives such as ketoconazole, itraconazole and fluconazole can result in impairment of clearance of such drugs, which, in some cases, can be and clinically important. Hence, a possible interaction of celecoxib with itraconazole was tested in a controlled clinical pharmacokinetic study.

The purpose of this study was to see the effect of itraconazole at steady state serum levels on the pharmacokinetics of celecoxib in male healthy human volunteers. It is known that celecoxib is mainly metabolized by CYP2C9 [6] and there are some reports that itraconazole has minor CYP2C9 inhibitory activity apart from its known CYP3A4 inhibition [7–9]. Karim et al. reported that fluconazole is a major CYP2C9 inhibitor and decreases the metabolism of celecoxib while increasing the AUC by about 2 fold in healthy human volunteers. They also observed the effect of ketoconazole, an inhibitor of CYP3A4 on the pharmacokinetics of celecoxib and found no change in the metabolism of celecoxib upon its co-administration in healthy human subjects [10].

Like ketoconazole, itraconazole has minor CYP2C9 inhibitory activity apart from its CYP3A4 inhibition [4, 7, 11]. In another study, ketoconazole increased the elimination half-life and AUC of tolbutamide, a CYP2C9 probe, by 25 and 66% respectively in healthy human volunteers [12]. As celecoxib is a novel agent and it is essential to investigate possible drug-drug interactions for establishing the safety and efficacy in humans.

The mean (s.d) serum concentrations of celecoxib (200 mg) with placebo and in combination with itraconazole (100 mg twice daily for 3 days) at different time points were determined. The pharmacokinetic parameters of celecoxib with placebo and in combinations with itraconazole are given in the Table.

In the presence of itraconazole, the mean C_{max} was altered from 449.3 ± 175 ng/ml to 527.81 ± 156 ng/ml, the mean $AUC_{0\text{-}t}$ increased from 4449.94 ± 1192 ng · h/ml to 4594.71 ± 1127 ng · h/ml, while the $AUC_{0-\infty}$ increased from 4735.78 ± 1243 ng · h/ml to 4821.93 ± 1262 ng · h/ml. The mean $t_{1/2}$ changed from 12.14 ± 3.52 h to 11.34 ± 6.71 h; the mean Cl/f decreased from 42.23 ± 9.63 to 40.39 ± 13.05 L/h; Vd/f decreased from 739.78 ± 175 to 678.22 ± 277 L/kg.

Table: Mean (S.D) (n = 12) of pharmacokinetic parameters of 200 mg oral celecoxib in human volunteers after placebo or 100 mg itraconazole twice daily for three days and single dose for concomitant administration on day 4

Pharmacokinetic parameter	With placebo	With itraconazole	Power value (at $\alpha = 0.05$)
C_{max} (ng/ml)	501.6 (280)	527.9 (245)	0.9
t_{max} (h)	2.75 (0.96)	2.5 (0.79)	0.9
$AUC_{(0\text{-}t)}$ (ng · h/ml)	4450 (1192)	4595 (1127)	1.0
$AUC_{(0\text{-}\infty)}$ (ng · h/ml)	4736 (1243)	4822 (1262)	1.0
$t_{1/2}$ (h)	12.1 (3.52)	11.3 (6.71)	0.1
Cl/f (L/h)	42.2 (9.63)	40.4 (13.05)	0.4
Vd/f (L/kg)	740 (175)	678 (277)	0.4

Paired t- test.

There was no statistically significant difference in any of the calculated pharmacokinetic parameters of celecoxib with placebo and in combination with itraconazole in male healthy human volunteers. The calculated power values were more than 0.9 or 90% to C_{max}, t_{max} and AUC where as the values were less than 0.8 or 80% to $t_{1/2}$, Cl/f and Vd/f (Table). The mean serum concentration patterns of celecoxib at various time points, with placebo or with co-administered itraconazole were almost superimposable.

Hence, in the present study, itraconazole (100 mg twice daily for 3 days) did not produce statistically significant changes on the pharmacokinetics of celecoxib in male healthy human volunteers. The metabolism of celecoxib is not inhibited by the co-administration of itraconazole, indicating that the CYP2C9 inhibitory activity of itraconazole is not proven to be significant in healthy human volunteers.

Experimental

1. Subjects

Twelve healthy male volunteers with a mean age of 27.3 ± 4.3 years (range 23 to 31 years) mean height of 164.4 ± 4.0 cm (range 160 to 170 cm) and mean weight of 61.8 ± 6.6 kg (range 54 to 70 kg) participated in the study after undergoing a thorough physical examination. The local ethics committee approved the study protocol.

2. Study design

A controlled 2×2 crossover study was conducted in 12 healthy male volunteers. After an overnight fast (approximately 12 h) each volunteer received celecoxib 200 mg (Revebra 200®, Dr. Reddy's Laboratories, Hyderabad, India) with placebo. One week washout period was given to the subjects. Then, twice daily dose of itraconazole 100 mg (Canditral 200® capsules, Glenmark Pharmaceuticals Ltd., Nasik, India) was given for three consecutive days. On day 4, celecoxib 200 mg was given with 100 mg of itraconazole.

3. Blood sampling and drug analysis

About 5 ml venous blood samples were drawn from the antecubital vein at 0, 0.5, 1, 2, 3, 4, 8, 12, 24, 36 and 48 h after drug administration. Serum was separated and stored at −20 °C until the analysis was performed. Celecoxib in the serum samples was estimated by reverse phase HPLC [6].

4. Pharmacokinetic data analysis

Pharmacokinetic parameters like peak plasma concentration (C_{max}), time to reach peak concentration (t_{max}), area under the celecoxib serum concentration time curve (AUC), elimination half-life ($t_{1/2}$), volume of distribution

(Vd/f) and total clearance (CL/f) for celecoxib were obtained for each subject using a computer program KINETICA (1999 Inna Phase Corporation) intended for calculation of model independent parameters. In the present study, $AUC_{(0-t)}$ refers to the AUC from 0 to 48 h and $AUC_{(0-\infty)}$ refers to the AUC from 0 to infinite time. C_{max} and t_{max} were determined as the highest observed concentrations and the time to reach the maximum concentrations, respectively. Elimination half life ($t_{1/2}$), area under the serum concentration curve (AUC), volume of distribution (Vd/f) and clearance (Cl/f) were calculated using non-compartmental model.

5. Statistical analysis

The resulting means of various pharmacokinetic parameters obtained in different subjects were compared using Student's t-test (paired data). A value of $p < 0.05$ was considered to be statistically significant.

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Changes in heart rate after application of newly developed ultrashort acting beta-adrenergic blockers

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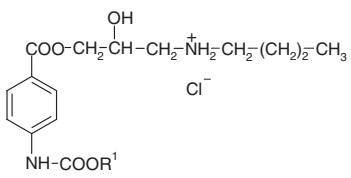
Antagonists of adrenergic β-receptors are widely used ischemic heart disease, hypertension, arrhythmias and hypertrophic cardiomyopathy [1–5]. Adverse effects of classical beta-blockers include hypotension, bradycardia, heart failure, bronchospasm, or peripheral vasoconstrictions, which can last up to several hours after intravenous application [6]. For this reason, beta-adrenoreceptor antagonists with an ultrashort duration of action are being developed [7].

The objective of our pilot study was to test the effect of three newly synthesised compounds on the physiological level (baseline) of a laboratory rat's heart rate. The compounds (derivates of arylcarbonyloxyaminopropanols) are substituted by a linear alkyl chain in the aliphatic part of the molecule – by ethyl in the substance 42 Bu, by propyl in 43 Bu and by butyl in 44 Bu [8, 9] (Table 1). Solubility and lipophility of the corresponding compounds also correspond with the chain length. In all three tested substances, a statistically proven short-acting bradycardic effect was detected. The onset of action of the substances tested was very fast. Inmediately in the first minute following application, a statistically highly significant bradycardic effect was noted in all three substances. Heart rate changes are given in Table 2.

The biggest significant decrease in heart rate ($13.00 \pm 5.53\%$) in comparison with the other two compounds showed the substance 44 Bu. The duration of the bradycardic effect was demonstrably longer in this sub-

Table 1: Chemical structures of the substances tested



Tested substance	R^1	T.t. (°C)	Solvent	R_F*
42 Bu	C_2H_5	120–123	Propan-2-ol	0.61
43 Bu	C_3H_7	116–119	Propan-2-ol	0.65
44 Bu	C_4H_9	109–112	Propan-2-ol	0.69