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Research Paper

Single-dose pharmacokinetics and safety of iptakalim hydrochloride in Chinese healthy volunteers

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Keywords
food effect; iptakalim; pharmacokinetics; phase I; safety

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Abstract

Objectives To investigate the safety, pharmacokinetics and food effect of iptakalim in healthy adult Han Chinese volunteers.

Methods Study 1 was a randomized open-label, Latin square designed, single-dose, three-period, self-control crossover study. Six men and six women received 5, 10 and 20 mg of iptakalim orally. Study 2 was a randomized, open-label, single-dose, two-period, self-control crossover study. Ten men were included and each subject received 5 mg iptakalim orally, fasting and nonfasting.

Key findings No adverse effects were reported and no clinically meaningful changes in vital signs were found. Cmax, AUC_{0-t} and $AUC_{0-\infty}$ were proportional over the dose levels of 5, 10 and 20 mg. Tmax, t½ and CL/F were similarly independent of dose level. In the 5 mg and 20 mg group, the Cmax, AUC_{0-t} and $AUC_{0-\infty}$ in women were significantly higher than in men, although they showed no difference after correction by mg/kg doses in the 5 mg group. At the 5-mg dose level, no significant difference in pharmacokinetics was found in nonfasting and fasting subjects.

Conclusions Single-dose pharmacokinetics of iptakalim showed dose proportionality over the dose levels of 5–20 mg. The pharmacokinetics showed gender differences in the 5 and 20 mg groups. Food had almost no impact on the pharmacokinetics at the 5 mg level.

Introduction

Iptakalim, 2,3-dimethyl-*N*-(1-methylethyl)-2-butanamine is a recently developed selective ATP-sensitive potassium channel opener (K_{ATP}CO),[1] which has undergone substantial pharmacological, biochemical and electrophysiological studies. It selectively regulates the pore of the inward rectifier potassium channel and dilates smaller arteries, but has little effect on dilatation of the aorta.[2] Animal studies reported that activation of K_{ATP} channels by iptakalim could increase the value of current density, attenuate pulmonary resistance vascular remodelling, control pulmonary hypertension of chronic hypoxic rat and inhibit the proliferation of pulmonary arterial smooth muscle cells induced by endothelin-1.[3–6] Its antihypertensive effects have been reported in spontaneously hypertensive rats and renal hypertensive dogs.[1,7] Iptakalim was found to have a protective effect on endothelial cells by activating K_{ATP} though preferential activation of the SUR2B/Kir6.1 subtypes of K_{ATP} expressed in endothelium, without activation of SUR1/Kir6.2 in the pancreas or in dopaminergic neurons of the brain.[2,8,9] Gao *et al.* showed that iptakalim possesses antihypertrophic properties, preventing the progression of left ventricular hypertrophy to heart failure induced by pressure overload.[10] Iptakalim protected the endothelium and prevented progression of cardiac hypertrophy to failure induced by a pressure overload.[11] Collectively, iptakalim has selective antihypertensive effects in hypertensive animals and does not induce tolerance, but has little effect on blood pressure in normotensive animals.[2,12,13] Meanwhile, it also reverses cardiovascular remodelling[10] and protects the brain and kidney against damage caused by hypertension in animal models.[2]

Given the potential utility of iptakalim in antihypertension therapy, there is clearly a need for further safety and pharmacokinetic data in humans. A tolerability research of a single dose of iptakalim hydrochloride has found that a dosage range of 2.5–25 mg was safe and tolerable in 52 healthy Chinese volunteers.[14] The aims of this study were to

determine the clinical pharmacokinetics of iptakalim following single oral dose administration in healthy human subjects. The effect of food on the pharmacokinetics of iptakalim was also investigated here. Our results will provide necessary data for new drug approval in China.

Materials and Methods

Inclusion and exclusion criteria

Eligible subjects were Han Chinese men or women, aged 18–40 years, who had a body mass index of 19–24 kg/m^2, with a permissible body weight of 50–80 kg (inclusive). Eligible participants were required to have a normal medical history, physical examination, clinical laboratory panel, and electrocardiogram. Subjects were excluded if any of the following criteria were met: (1) personal history of cardiac, nervous, ocular or endocrine disease; (2) personal history of hypersensitivity, especially to medicine or foods; (3) any significant clinical or laboratory abnormality; (4) positive for HIV or HBsAg examination; (5) undergone blood donation within a month of study initiation or intended to donate blood a month after study; (6) evidence of drug, alcohol and cigarette abuse (light smokers included, smoking index (SI) = the number of cigarettes smoked per day × smoking years, SI $\leq$200 were light smokers); (7) subjects had taken experimental medication within four months of study enrollment; (8) subjects taken prescription or over-the-counter medicines within three weeks of study enrollment; (9) women who were nursing or who intended to be pregnant or were menstruating; and (10) anyone who considered that they could not complete the study for any reason.

This study was conducted in accordance with principles of Good Clinical Practice[15] and the Declaration of Helsinki[16] and was approved by China State Food and Drug Administration (No. 2003L03831) and the Ethics Committee of People's Liberation Army (PLA) general hospital (2005LS029). All study participants were given informed consent form and consent was obtained before undergoing any study-related procedures.

Study design

Iptakalim hydrochloride tablets (5 mg iptakalim/tablet, batch number 20040301, production date: March, 1 2004. Validity: 2 years.) were from Xuzhou Yan Hua Pharmaceutical Group Co., Ltd (Xuzhou, China). Production conditions met the GMP requirements; all tablets had drug qualified certification.

Study 1 was an open-label, Latin square designed, single-dose, three-period, self-control crossover study to compare the pharmacokinetics of three different doses of iptakalim when orally administered to fasting, healthy male and female volunteer subjects. Six men and six women received 5 mg, 10 mg and 20 mg of iptakalim. The order of administration was randomized and each dose was separated with a seven-day washout period.

Study 2 was designed as a randomized, open-label, single-dose, two-period, self-control crossover study to compare the pharmacokinetics of iptakalim under fasted and fed conditions. Ten men were included and each subject received 5 mg iptakalim orally fasting and nonfasting. The order of administration was randomized and each dose was separated by a washout period of seven days.

Testing field was located at Unit of Phase I Clinical Trial of National Institute of Clinical Trial For Drugs in PLA General Hospital. Participants were hospitalized at 2000 h the day before study, and had two pieces of whole-wheat bread at 2100 h, and then no food but water was allowed for 11 h. The next day, they received an oral dose of iptakalim with 200 ml water on an empty stomach, at approximately 0800 h. They were allowed to take standard breakfast (120 g bread, one egg, 250 ml porridge; total about 650 calories) at approximately 0900 h. Water was allowed after 1000 h. In study 2, subjects in the nonfasting group received their doses after a standard high-fat breakfast (50% fat calories, 15% protein calories, 35% carbohydrates calories; total about 800 calories). They consumed the meal within 25 min, and iptakalim was administered within 5 min of meal completion. During the course of the study, the participants were allowed to take 100 ml water per hour to maintain urine and refrained from aggravating activity, tea, coffee, coffee drinks and other medications.

Safety assessment

Safety measures included vital sign measurements (heart rate, respiration rate, body temperature and blood pressure), physical examination, ECG and EEG, and clinical laboratory testing (routine blood test, blood biochemistry, routine urine test, hepatic function, renal function, fundus examination). Any adverse event observed by the investigator or reported by the subject during the study period was recorded. Adverse events were tabulated by body system or organ class, severity and relationship to the study medication, and summarized by treatment assignment. The researchers were responsible for recording vital signs and offered first aid if an emergency arose. Throughout the study, a certified physician who was totally free of conflicts of interest regarding this trial was responsible for the care of subjects. Vital signs were assessed at screening and in the morning (before taking study medication when it was a dosing day) on each day of study. Clinical laboratory testing, ECG, EEG and fundus examinations were obtained at screening, pre-dose day of first period and post-dose day of last period.

Pharmacokinetic assessment

Blood samples for plasma drug concentration determinations were collected before dosing and at 0.0833, 0.17, 0.33,

0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 and 30 h after oral administration. Indwelling catheters were used and 2 ml of 0.9% physiological saline was used to flush lines after sample collection. When collecting a blood sample, 3 ml blood was discarded to avoid the effect of physiological saline. A 4-ml sample was collected at each time point and processed within 30 min. Samples were centrifuged for 10 min at approximately 4°C and 1500*g*. Plasma samples were immediately frozen to −80°C or below and kept frozen until assayed. Urine sample were collected at 2, 4, 6, 8, 12, 24 and 36 h; the volume of urine for each period were recorded and 4 ml urine from each period was also stored at −80°C. The analytical method was based on liquid chomatography–tandem mass spectrometry (LC-MS/MS) using sildenafil as internal standard.[17] Sample preparation involved liquid–liquid extraction with dichloromethane–diethyl ether (2 : 3, v/v) in a basic environment. Chromatography was carried out on an amino column with a mobile phase consisting of acetonitrile–water (55 : 45, v/v; water containing 0.5% formic acid). Detection employed electrospray ionization (ESI) tandem mass spectrometry in the multiple-reaction-monitoring (MRM) mode. The assay was linear in the concentration range of 0.5–100 μg/l with a lower limit of quantitation (LLOQ) of 0.5 μg/l. Intra-day and inter-day precision (RSD) were <4.5% and <12.0%, respectively, and the accuracy (RE) was in the range ±5%.

Pharmacokinetic evaluation and statistical analysis

Pharmacokinetic parameters were derived by noncompartmental analysis using WinNonlin 5.2.1 (Pharsight Corp., Mountain View, USA). All parameters were calculated on an individual subject basis and summarized for each dose level. Descriptive statistics were used to summarize the following pharmacokinetic parameters: C_{max}, peak plasma concentration; T_{max}, time of maximum concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the concentration-time curve from time zero to the last measurable concentration; k, elimination rate constant; $T_{1/2}$, elimination half-life; Vd/F, volume of distribution; CL/F, total body clearance; MRT, mean residence time. Linear-log trapezoidal rule was used as a calculation method for AUC. In study 1, one-way analysis of variance with dose-normalized values was used to evaluate the dose linearity of Cmax and AUC for iptakalim. Analysis of variance was also used to evaluate any difference in $T_{max,}$ t½ and CL/F between the dose groups. Difference in pharmacokinetic parameters between males and females in the same dose group was evaluated by paired *t*-test. In study 2, the 90% confidence intervals (CIs) for differences in Cmax, $AUC_{0-\infty}$ andAUC_{0-t} were calculated and T_{max} was analysed using a Wilcoxon matched pairs test at 5 mg dosage to evaluate the effect of food.

Results

Study population

Of 12 (6 female and 6 male) and 10 (male) healthy volunteers in each study, all completed treatment phases. All subjects ranged from 20 to 36 years of age. Mean age and body mass index (BMI) were similar in males and females taking part in study 1. All subjects were Han Chinese. A summary of the demographic characteristics of the subjects is presented in Table 1.

Safety profile and tolerability

Single doses of iptakalim were generally well tolerated throughout the study. No serious adverse events were observed, and no drug-related adverse events were reported. No subjects were withdrawn from the study, and no dose-related changes or trends in clinical laboratory values were noted. Total protein (before vs after administration: 76.67 ± 3.91 vs 72.93 ± 3.90 g/l, range of normal values: 55–80 g/l), Cl^- (103.25 ± 2.35 vs 105.35 ± 2.08, 94–110 mmol/l), Ca^{2+} (2.37 ± 0.14 vs 2.68 ± 0.08, 2.25–2.75 mmol/l), and glutamic-oxaloacetic transaminase (GOT) of blood biochemistry (26.69 ± 5.16 vs 19.80 ± 5.48, 0–40 U/l) showed significant difference after administration compared with before administration; however, they were all within normal limits and had no clinical significance. There were no clinically meaningful changes in vital signs. ECG, EEG and eye examination did not reveal any clinically significant changes. Blood pressure did not obviously change (the difference in pressure after and before administration was less than 10 mmHg, both for systolic and diastolic pressure) after a single dose of 5, 10 and 20 mg iptakalim (Figure 1).

Table 1 Baseline characteristics of study population

	Study 1			Study 2
	Men (6)	Women (6)	All (12)	Men (10)
Age (years)	26.5 ± 2.57	28.33 ± 1.66	27.41 ± 2.27	28.25 ± 0.75
Height (cm)	174 ± 2.61	159.17 ± 3.81	166.58 ± 8.35	171.7 ± 3.74
Weight (kg)	65.42 ± 3.26	57.83 ± 4.49	61.63 ± 5.45	68.1 ± 5.11
Range of weight (kg)	61.00–69.50	50.00–62.00	50.00–69.50	62.00–74.00
Body mass index (kg/m^2)	21.61 ± 0.90	22.79 ± 0.80	22.20 ± 1.02	23.13 ± 2.03

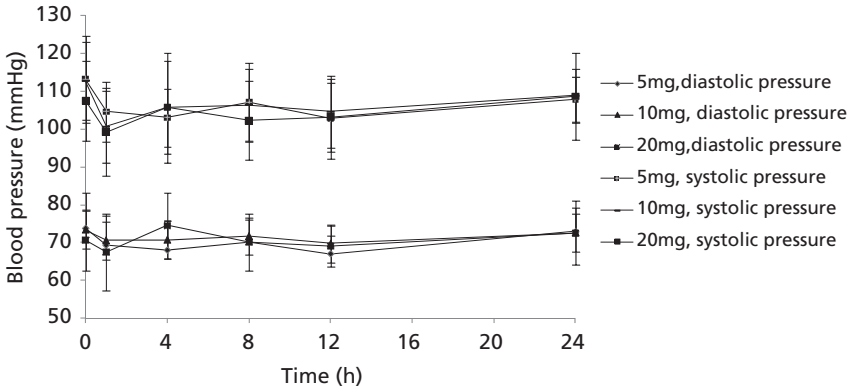

Figure 1 Mean blood pressure (diastolic, systolic pressure) before and after single-dose administration of 5, 10 and 20 mg iptakalim. Error bar, SD.

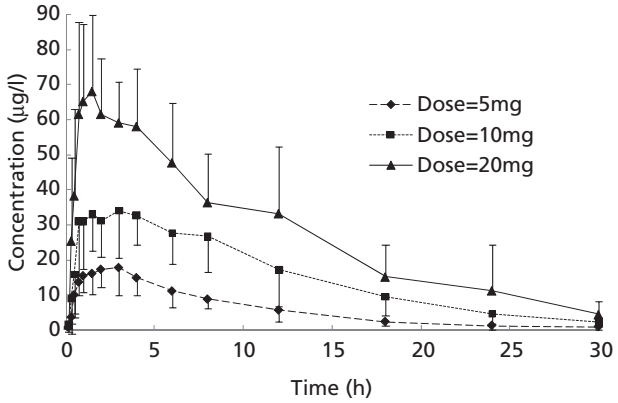

Figure 2 Mean plasma iptakalim concentration–time profiles following single-dose administration. Symbols represent oral administration of iptakalim at 5 mg (diamonds), 10 mg (squares) and 20 mg (triangles) to fasting volunteers. Linear range, 0.5–100 μg/l; LLOQ, 0.5 μg/l; error bar, SD. All the subjects received breakfast at 1 h.

Pharmacokinetics analysis

In study 1, Figure 2 shows the plasma concentration-time profile of iptakalim after 12 healthy volunteers' oral single-dosage 5 mg, 10 mg and 20 mg. Arithmetic means and standard deviation of pharmacokinetic parameters are presented in Table 2. No iptakalim levels were measured in the pre-dose sample. Plasma Cmax was proportional over the dose levels of 5, 10 and 20 mg (Table 2). Median Tmax values were relatively similar across all different dose groups, suggesting little dose effect on Tmax. The median t½ values were also relatively similar in the fasting 5, 10 and 20 mg dose groups, respectively. Similar to the Cmax results, AUC_{0-t} and $AUC_{0-\infty}$ were 171.37/181.99, 469.13/491.88 and 891.84/945.72 h μg/l over the dose levels of 5, 10 and 20 mg, and there seemed to be no deviation from dose proportionality. Apparent plasma clearance (CL/F) and apparent volume of distribution (V/F) were independent of dose for the 5, 10 and 20 mg dose levels. No difference in pharmacokinetic parameters was found between dose groups.

In the 5 mg group, the C_{max} (25.23 vs 17.97 μg/l), T_{max} (2.17 vs 1.50 h) and AUC_{0-t} (202.02 vs 140.72 h μg/l), $AUC_{0-\infty}$ (217.94 vs 146.04 h μg/l) in women were significantly higher than in men ($P < 0.05$), while the CL/F (25.69 vs 35.93 ml/h) in women was lower than in men ($P < 0.05$). In the 20 mg group, the AUC_{0-t} (1158.64 vs 625.03 h μg/l), $AUC_{0-\infty}$ (1244.63 vs 646.80 h μg/l) and CL/F (17.50 vs 32.09 ml/h) showed significant difference between women and men ($P < 0.01$). However, when the C_{max} and AUC were corrected by mg/kg doses given, no differences were found in the C_{max} (23.00 vs18.38 μg/l), AUC_{0-t} (179.81 vs 140.95 h μg/l), $AUC_{0-\infty}$ (194.09 vs 146.42 h μg/l) of the 5 mg group between women and men ($P > 0.05$), while the difference still existed in AUC_{0-t} (1020.56 vs 623.68 h μg/l) and $AUC_{0-\infty}$ (1097.03 vs 645.76 h μg/l) in the 20 mg group ($0.01 < P < 0.05$).

Accumulative urinary excretory rates (total amount of iptakalim excreted in urine/dosage given) for the different dose are shown in Table 3. Iptakalim can be detected as unchanged drug in urine samples (which were collected from 0 to 36 h after dose). After 36 h, most iptakalim (59.78–72.32%) was excreted through the kidneys.

In study 2, pharmacokinetic parameters after an oral single dose of 5 mg iptakalim given to fasting and nonfasting men are presented in Table 4. Mean plasma concentration–time (±SD) profiles are shown in Figure 3. At the 5-mg dose level, nonfasting subjects had a little higher Cmax (34.59 vs 30.13 μg/l), AUC_{0-t} (271.53 vs 246.26 h μg/l) and $AUC_{0-\infty}$ (290.66 vs 259.76 h μg/l) values than fasting subjects did but lower t½ (6.31 vs 6.89 h), T_{max} (1.33 vs 1.50 h), CL/F (18.86 vs 20.52 ml/h) and V/F (167.97 vs 199.26 ml) than fasting subjects did (median values are given). The 90% CIs upper limits were <125%, 110.91% for Cmax, 104.82% for AUC_{0-t} and 104.98% for $AUC_{0-\infty}$. The lower limits of the 90% CI for Cmax, AUC_{0-t} and $AUC_{0-\infty}$ were 98.31%, 98.60% and 98.79%,

Table 2 Comparison of pharmacokinetic parameter for different single doses of iptakalim in 12 volunteers (Study 1)

	5 mg			10 mg			20 mg		
Parameter	Men	Women	All	Men	Women	All	Men	Women	All
K (1/h)	0.13 ± 0.02	0.12 ± 0.04	0.13 ± 0.03	0.11 ± 0.01	0.12 ± 0.03	0.11 ± 0.02	0.12 ± 0.02	0.12 ± 0.05	0.12 ± 0.04
t½(h)	5.58 ± 0.82	6.53 ± 3.33	6.05 ± 2.37	6.60 ± 0.83	6.07 ± 1.55	6.33 ± 1.22	6.04 ± 0.86	7.11 ± 3.80	6.58 ± 2.68
C_{max}(μg/l)	17.97 ± 3.72	25.23 ± 6.61*	21.60 ± 6.37	43.03 ± 8.69	45.43 ± 6.10	44.23 ± 7.27	75.17 ± 12.99	86.55 ± 18.97	80.86 ± 16.60
C_{max}(μg/l) corrected	18.38 ± 3.96	23.00 ± 6.59	20.69 ± 5.72	43.77 ± 7.93	40.99 ± 6.11	42.38 ± 6.90	76.79 ± 13.09	78.43 ± 19.12	77.61 ± 15.65
T_{max}(h)	1.50 ± 0.55	2.17 ± 0.13*	1.83 ± 0.86	1.04 ± 0.49	1.96 ± 0.95	1.50 ± 0.87	1.38 ± 0.89	1.63 ± 0.80	1.50 ± 0.82
AUC_{0-t} (h μg/l)	140.72 ± 32.19	202.02 ± 64.86*	171.37 ± 58.38	388.72 ± 173.88	549.54 ± 117.92	469.13 ± 164.67	625.03 ± 115.20	1158.64 ± 374.79**	891.84 ± 384.11
AUC_{0-t} (h μg/l) corrected	140.95 ± 34.03	179.81 ± 61.82	160.38 ± 51.72	384.51 ± 165.66	483.09 ± 98.20	433.80 ± 139.67	623.68 ± 118.41	1020.56 ± 310.33*	822.12 ± 305.14
$AUC_{0-\infty}$ (h μg/l)	146.04 ± 33.19	217.94 ± 80.53*	181.99 ± 69.70	405.78 ± 183.87	577.97 ± 127.25	491.88 ± 175.54	646.80 ± 124.58	1244.63 ± 478.24**	945.72 ± 456.61
$AUC_{0-\infty}$ (h μg/l) corrected	146.42 ± 35.23	194.09 ± 75.36	170.26 ± 61.36	401.69 ± 175.27	508.76 ± 107.69	455.22 ± 149.54	645.76 ± 127.65	1097.03 ± 397.55*	871.40 ± 367.13
Cl/F (ml/h)	35.93 ± 9.17	25.69 ± 9.32*	30.81 ± 10.31	28.19 ± 10.00	18.10 ± 4.42	23.14 ± 9.06	32.09 ± 7.38	17.50 ± 4.57*	24.80 ± 9.61
V/F(ml)	275.17 ± 79.49	225.93 ± 80.82	259.21 ± 83.96	252.99 ± 89.93	160.50 ± 48.19*	215.53 ± 89.64	269.50 ± 55.30	160.68 ± 34.83*	221.34 ± 77.17
MRT (h)	8.52 ± 1.00	9.21 ± 2.84	8.87 ± 2.06	9.59 ± 1.31	10.87 ± 2.36	10.23 ± 1.94	8.77 ± 1.54	11.81 ± 3.03	10.29 ± 2.79

*$P < 0.05$, compared within the same dosage in men's group, **$P < 0.01$, compared within the same dosage in men's group. Corrected, values were corrected by mg/kg doses given

Table 3 Accumulative urinary excretory rate (Study 1)

	Accumulative urinary excretory rate (%)		
Time (h)	5 mg	10 mg	20 mg
2	10.77 ± 2.77	7.75 ± 2.24	3.61 ± 1.10
4	22.97 ± 3.72	20.34 ± 3.65	17.39 ± 2.93
6	31.74 ± 4.71	28.26 ± 4.99	22.33 ± 3.15
8	38.76 ± 4.49	33.57 ± 5.32	28.75 ± 5.01
12	50.37 ± 4.41	42.34 ± 5.42	43.46 ± 6.50
24	64.19 ± 5.89	56.76 ± 6.18	61.40 ± 5.59
36	67.42 ± 5.67	59.78 ± 4.91	72.32 ± 6.15

Table 4 Comparison of pharmacokinetics parameter of a single 5 mg dose of iptakalim in 10 volunteers between fasting and nonfasting state (Study 2)

Parameter	Nonfasting	Fasting
k (h^{-1})	0.11 ± 0.02	0.11 ± 0.03
$t_{1/2}$ (h)	6.31 ± 1.37	6.89 ± 2.24
T_{max} (h)	1.33 ± 1.06	1.50 ± 0.94
C_{max} (μg/l)	34.59 ± 8.67	30.13 ± 7.76
AUC_{0-t} (h μg/l)	271.53 ± 85.30	246.26 ± 60.03
$AUC_{0-\infty}$ (h μg/l)	290.66 ± 94.57	259.76 ± 63.73
Cl/F (ml/h)	18.86 ± 6.12	20.52 ± 5.91
V/F(ml)	167.97 ± 37.92	199.26 ± 51.92
MRT (h)	9.23 ± 1.17	9.24 ± 1.37

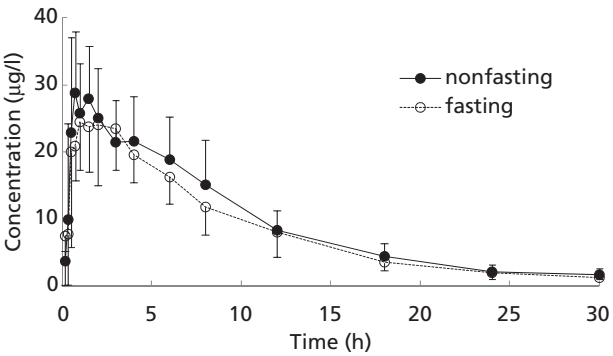

Figure 3 Mean plasma drug concentration in both fasting and nonfasting states. Symbols represent oral administration of 5 mg iptakalim in fasting (empty circle) and nonfasting (filled circle) states. Linear range, 0.5–100 μg/l; LLOQ, 0.5 μg/l; error bar, SD. Subjects in nonfasting group received breakfast at –0.5 h. Subjects in fasting group received breakfast at 1 h.

respectively, both higher than the 80% acceptance criterion. Result of Wilcoxon matched pairs test for T_{max} also showed no difference between fasting and nonfasting groups ($P > 0.05$).

Discussion

This was the first study that assessed the plasma pharmacokinetics and food effect of iptakalim. Single doses ranged from

5 mg to 20 mg; and in combination with food, 5 mg to healthy subjects. The single-dose plasma pharmacokinetics of iptakalim in fasting subjects showed dose proportionality over the dose levels of 5, 10 and 20 mg. Most of the iptakalim was excreted as unchanged drug in the urine. At the 5-mg dose level of iptakalim, nonfasting subjects showed almost the same C_{max}, T_{max}, t½ and AUC as fasting subjects (Table 4).

The safety data indicate that iptakalim was generally well tolerated. Throughout the study, no serious adverse events and no drug-related adverse events were reported. There were no clinically meaningful changes in vital signs. ECG, EEG and fundus examination did not reveal any clinically significant changes. Some indices of blood biochemistry (total protein, Cl^-, Ca^{2+}, and GOT) showed statistically significant change after dosing in individual subjects, although the values were still within normal limits and had no clinical significance. Both systolic and diastolic pressure did not show obvious change after dose. Previous studies have reported that iptakalim has selective and long-lasting antihypertensive effects in hypertensive animals and does not induce tolerance, but has no effect on blood pressure in normotensive animals.[2,12,13] Our study also indicated that a single dose of iptakalim might have no effect in normotensive humans. However, both published data on animals and our phase I study only evaluated the effect of a single dose of iptakalim in normotensive subjects. Continuous dosing effects in normotensive subjects are still unknown and need further research.

Following single doses, iptakalim was readily absorbed, reaching the C_{max} between 1.0 and 2.5 h postdose (fasted conditions). Thirty-six hours later, most iptakalim (59.78–72.32%) was excreted in urine as unchanged drug, also suggesting good oral absorption and bioavailability. AUC and C_{max} in the 5 mg and AUC in 20 mg groups were significantly different between men and women. Cl/F of iptakalim was obviously lower in women than in men at all three dose levels, so differences between the sexes in pharmacokinetics may be driven by a reduced elimination of the drug in women. When AUC and Cmax were corrected by mg/kg doses given, the difference reduced greatly or vanished. Therefore, we also speculated that the pharmacokinetic differences between men and women may be partly due to their weight categories. Although no data has been published on gender differences in any animal species, we cannot rule out the impact of gender on iptakalim elimination from this clinical trial. Considering the small sample sizes (6 male and 6 female) included here, close attention should be paid to gender differences in later studies on multiple doses or phase II clinical trials.

At the 5-mg dose level, almost the same C_{max} and AUC were seen in the nonfasting subjects as in the fasting subjects. As a medicine with a small molecular weight, iptakalim was reported to have good liposolubility and water-solubility.[1] A high-fat meal had almost no impact on the rate and extent of oral plasma exposure of iptakalim. However, the result was only based on a 5 mg dosage, so the dose-dependent effects of food need further research.

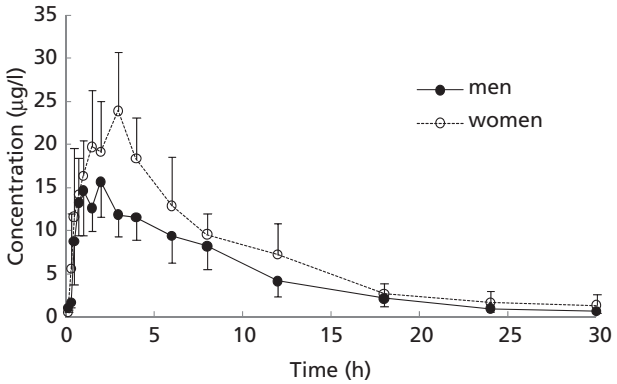

Figure 4 Mean plasma drug concentrations in men and women in the 5 mg iptakalim group. Symbols represent women (empty circle) and men (filled circle). Linear range, 0.5–100 μg/l; LLOQ, 0.5 μg/l; error bar, SD. All the subjects received breakfast at 1 h.

Two peaks were observed in some concentration–time curves in both study 1 (Figure 2 10 mg group, Figure 4 male and female groups) and study 2 (Figure 3 fasting and nonfasting groups). This indicates that enterohepatic recirculation might occur. So, in addition to excretion through the kidneys, part of iptakalim is likely excreted through the bile.

There are three limitations of this pharmacokinetics-focused clinical trial. First of all, food was taken 1 h after oral dosing in study 1, which was a short length of time and might cause a potential risk of food influence on the pharmacokinetics. Fortunately, the following food effect study confirmed that no effect existed at the 5 mg dosage. However, whether food has an effect on pharmacokinetics at higher dosages is unknown. Secondly, because differences in pharmacokinetics were found between men and women, while the food effect study only included men, it is not clear whether food has any effect on the pharmacokinetics of iptakalim in women. The third limitation was that total iptakalim was detected in this study and the study was not designed to detect unbound drug exposure. Since only unbound drug is effective, we were not able to provide the information here.

Conclusions

In conclusion, iptakalim appears safe when administered orally as a single dose to this small selected group of healthy normal volunteers in a fasting state (5–20 mg) or nonfasting state (5 mg). The single-dose plasma pharmacokinetics of iptakalim in fasting subjects showed dose proportionality over the dose range of 5–20 mg. The pharmacokinetics showed apparent sex differences for the 5 and 20 mg groups.

Food had almost no impact on the pharmacokinetic parameters of 5 mg iptakalim in male volunteers.

Declarations

Conflict of interest

Dr Rui Wang is the principal investigator of this clinical trial. Dr Hai Wang owns the patent of iptakalim. Other authors have no financial disclosures or conflicts of interest to report.

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