

Pharmacokinetics, Safety and Tolerability of Bencycloquidium Bromide, a Novel Selective Muscarinic M1/M3 Receptor Antagonist, After Single and Multiple Intranasal Doses in Healthy Chinese Subjects

An Open-Label, Single-Center, First-in-Human Study

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Abstract

Background: Bencycloquidium bromide (BCQB) is a novel, potent and selective muscarinic M1/M3 receptor antagonist under development for the treatment of rhinorrhea in rhinitis. The pharmacokinetics and safety of BCQB in animals have been established in preclinical studies. However, no clinical pharmacokinetic data are available for BCQB in humans.

Objective: The aim of this first-in-human study was to evaluate the pharmacokinetics, safety and tolerability of BCQB following single and multiple intranasal doses in healthy Chinese subjects.

Methods: The clinical trial was comprised of the following four studies: (i) an open-label, single-dose escalation study to evaluate the safety and tolerability in healthy subjects after intranasal doses of BCQB ranging from 45 to 450 µg (total of six doses); (ii) an open-label, multiple-dose escalation study to assess the safety and tolerability in healthy subjects after intranasal administration with 120 and 150 µg doses of BCQB (360 and 450 µg/day) administered three times daily for 15 days; (iii) a randomized, open-label and parallel-group design to evaluate the single-dose pharmacokinetics of BCQB after intranasal dosing (45, 90, and 180 µg); and (iv) ten subjects received 120 µg of BCQB by intranasal administration, three times daily for 5 days with a final single dose on day 7 to assess its multiple-dose pharmacokinetics. Safety and tolerability of BCQB were evaluated by monitoring adverse events (AEs), ECG

recordings, vital signs and clinical laboratory parameters. The pharmacokinetic parameters for BCQB were calculated by software using non-compartmental methods.

Results: All AEs were mild, of limited duration and no more frequent at higher doses. There was no serious adverse event, death or withdrawal. No clinically significant change was noted in clinical laboratory parameters, cardiac parameters or vital signs. Following single intranasal dosing, BCQB was rapidly absorbed with a median time to maximum concentration (t_{\max}) of 8 minutes for 45, 90, and 180 μg dose groups; the plasma concentration of BCQB decreased in a biphasic manner with the mean half-life ($t_{1/2}$) of 8.5 hours; the maximum concentration (C_{\max}) and area under the plasma concentration-time curve (AUC) of BCQB increased linearly across the examined dose range of 45–180 μg . During the multiple dosing, the steady state was achieved within 3 days of 120 μg three times daily dosing of BCQB. A slightly greater AUC was observed after 5 days of multiple dosing, with the mean accumulation ratio of 1.26; however, the half-life was unchanged.

Conclusion: BCQB was safe and well tolerated in healthy Chinese subjects when administered intranasally with single and multiple doses across the doses studied. The mean C_{\max} and AUC increased proportionally to the studied doses, and the steady state was achieved within 3 days after three times daily dosing. A slight accumulation of BCQB following multiple dosing was observed. The pharmacokinetics, safety and tolerability profiles of BCQB pose it as a good candidate for further development in the treatment of rhinorrhea in rhinitis.

Introduction

Bencycloquidium bromide, 3-{(2-cyclopentyl-2-hydroxy-2-phenyl) ethoxy}-1-methyl-1-azabicyclo [2, 2, 2] octane bromide (BCQB, figure 1), is a novel selective muscarinic M1/M3 receptor antagonist for the treatment of rhinorrhea in rhinitis by intranasal administration. Rhinitis, an inflammation of the nasal mucous membrane, is one of the most common diseases, and is estimated to affect 10–40% of the global population with increasing prevalence in both children and adults.^[1,2] Currently, ipratropium bromide (IB) is the only muscarinic antagonist in clinical use for the treatment of rhinorrhea in rhinitis.^[3] However, the anticholinergic effect of IB is short-acting, and IB is less selective among the M1, M2, and M3 muscarinic receptors.^[4] Recently, long-term use of inhaled IB has been shown to be associated with an

increased risk of adverse cardiovascular outcomes in patients,^[5] which may be related to its action on the muscarinic M2 receptor in the heart. Given the high prevalence of rhinitis and the undesirable safety profile of IB, the development of additional options is clearly warranted. Many studies have shown that intranasal BCQB has good efficacy in the treatment of rhinitis especially rhinorrhea in preclinical studies.^[6–10] Additionally, BCQB displayed a better safety profile than IB

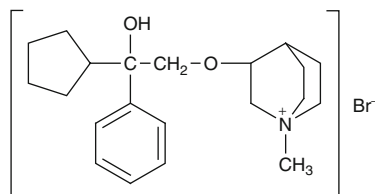


Fig. 1. Chemical structure of bencycloquidium bromide.

due to its high selectivity for the M1 and M3 receptors over the M2 receptor.^[11,12] As a result, M2 cardiac receptors are spared thereby reducing the risks of cardiovascular adverse events.^[13] Preclinical toxicity studies also showed no apparent change in the ECG or heart rate in dogs^[13] and rats.^[14] Our recent phase II clinical trial in China showed that intranasal administration of BCQB was effective in reducing rhinorrhea with few side effects. Preclinical studies described the pharmacokinetics, tissue distribution, excretion and metabolism of BCQB after intranasal dosing in rats^[15-18] or beagle dogs.^[19] However, no data are available on the pharmacokinetics, safety and tolerability of BCQB in humans. Therefore, as a first-in-human (FIH) clinical trial, this study was conducted to evaluate the safety, tolerability and pharmacokinetics of BCQB after single and multiple intranasal doses in healthy Chinese subjects.

Methods

The FIH clinical trial was performed at a single center (First Affiliated Hospital of Nanjing Medical University) in Nanjing, China. The study was approved by the Ethics Committee at this study center and was conducted in accordance with guidelines for the Declaration of Helsinki and Good Clinical Practice (GCP) in China. All subjects were informed of the investigational nature of this study, and signed an informed consent statement prior to the initiation of the study.

Subjects

All eligible subjects were men or women aged 20–50 years, and were of Chinese origin (table I). Subjects' health states were analyzed on the basis of medical history, physical examination, eye examination, laboratory examination, and ECG.

The following exclusion criteria were applied for subjects in this clinical trial: a history of clinically significant cardiovascular, renal, urinary tract, hepatic, pulmonary, gastrointestinal, eye, mouth, nose, or mucosal diseases that might interfere with absorption, distribution, metabolism, or excretion of BCQB; a history of nervous system

Table I. Summary of baseline demographics^a

Group	Safety assessment				Pharmacokinetic profile											
	Single dose (µg)				Multiple dose (µg)				Single dose (µg)				Multiple dose (µg)			
	45	90	180	270	360	450	120	150	45	90	180	45	90	180	120	
n	6	8	8	8	6	6	8	8	8	6	6	10	10	10	10	
Sex (F/M)	3/3	4/4	4/4	4/4	3/3	3/3	4/4	4/4	4/4	5/5	5/5	5/5	5/5	5/5	5/5	
Age (y)	38±10	35±8	37±6	35±9	30±5	35±8	30±8	31±7	31±7	26±4	27±5	26±4	27±5	26±3	28±5	
Weight (kg)	61±11	63±12	59±13	65±9	60±10	66±8	58±7	59±6	59±6	58±5	60±6	58±5	60±6	59±5	60±7	
Height (cm)	166±8	168±8	164±11	166±5	164±5	168±6	167±7	165±7	165±7	167±6	168±7	167±6	168±7	167±6	166±8	
BMI (kg/m ²)	22.0±2.5	21.9±2.9	22.0±2.3	23.7±2.4	22.2±3.0	23.3±2.1	20.7±1.1	21.6±1.1	21.6±0.7	20.8±0.8	21.0±1.1	21.1±0.8	21.0±1.1	21.1±0.8	21.6±1.1	

^a Data are expressed as mean ± SD (unless otherwise stated).

BMI = body mass index; **F** = female; **M** = male.

or muscle disease, seizure disorder or a psychiatric disorder that might hinder compliance with the study; a history of known allergy or intolerance to any drugs; a history of tobacco, alcohol or drug abuse; those with abnormalities in clinical laboratory parameters; those who had received an investigational drug, or donation of blood in the preceding 3 months, or had received any drug within 2 weeks before the study start date, or was considered by the investigator, for any reason, to be an unsuitable candidate for receiving BCQB. Females who were lactating or who had a positive pregnancy test were also ineligible.

Study Drug and Administration

BCQB nasal sprays used in these studies were manufactured by Beijing Shiqiao Biological and Pharmaceutical Co. Ltd (Beijing, China). The intranasal formulation provided different doses (22.5, 45, 60, 75, 90, 135, 180, and 225 µg) of BCQB in a 0.09 mL spray from a single-dose metered sprayer. The same metered sprayer (0.09 mL/spray)

with different drug loads was used in tolerability and pharmacokinetic studies. For intranasal administration, each subject received a single spray in each nostril, for a total of two sprays. For example, the dosage of 45 µg was provided by a spray of 22.5 µg/spray in each nostril (22.5 µg/spray × 2). Prior to the administration of BCQB, the subject gently blew his or her nose. A physician administered the nasal spray and attempted to concentrate the application on the lateral nasal wall, particularly along the inferior and middle turbinate mucosa, according to the standard operating procedures (SOPs).

Study Design

Single-Dose Escalation Tolerability Study

An open-label, single-dose escalation design was used to evaluate the safety and tolerability of BCQB after intranasal dosing (see table II). Subjects, 50% male and 50% female, were subsequently enrolled into the 45, 90, 180, 270, 360, and 450 µg dose groups (6–8 subjects in each

Table II. Study design

Period	Number ^a	Dose groups (µg)
Period 1 ^{b,c}	6	45
Single-dose escalation tolerability study	8	90
	8	180
	8	270
	6	360
	6	450
	8	120 tid for 14 days (360 µg/day)
Period 2 ^{b,c,d}	8	150 tid for 14 days (450 µg/day)
Period 3 ^e	10	45
	10	90
	10	180
Period 4 ^f	10	120 tid for 5 days
Multiple-dose pharmacokinetic study		

a The number of subjects in each dose group.

b An open-label, dose escalation design was used.

c The trial would not proceed to the higher dose group until the safety and tolerability of the lower dose group were confirmed.

d The trial began with the 120 µg dose group (360 µg/day), and this dosage was assigned according to the results of the single-dose tolerability study.

e A randomized, open-label and parallel-group design was used.

f Administrated on day 1; received no treatment on day 2; and continued to receive the study drug tid from days 3 through 7.

tid = three times daily.

group). The trial was designed to begin with the 45 µg dose group and would not proceed to the higher dose group until the safety and tolerability of the lower dose group was confirmed.

Multiple-Dose Escalation Tolerability Study

An open-label, multiple-dose escalation design was performed to begin with the 120 µg dose group (360 µg/day) according to the results of the single-dose tolerability study and would not proceed to the higher dose group (450 µg/day) until the safety and tolerability of the 360 µg dose group was confirmed (see table II). Subjects, 50% male and 50% female, were also subsequently enrolled into two dose groups (eight subjects in each), and were given 120 µg (360 µg/day) or 150 µg (450 µg/day) of BCQB via nasal spray three times daily (at 7:30am, 12:00pm and 7:00pm) for 14 days to assess its safety and tolerability.

Pharmacokinetic Study

A randomized, open-label and parallel-group design was used to evaluate the pharmacokinetic profile of BCQB after single intranasal dosing (see table II). Thirty healthy subjects, 50% male and 50% female, were randomized into 45, 90, and 180 µg dose groups (ten subjects in each) for the determination of the pharmacokinetic profile of a single-dose BCQB by the investigator. Another ten subjects, 50% male and 50% female, were administered 120 µg of BCQB by intranasal sprays on day 1; received no treatment on day 2; and continued to receive the study drug three times daily (at 7:30am, 12:00pm and 7:00pm) from days 3 through 7 to assess multiple-dose pharmacokinetics (see table II).

The subjects were required to fast overnight (12 hours) before administration, while standard meals and water intake were provided 2 hours post-dose. Blood samples (5 mL) were collected at 0 hours (pre-dose), 2, 5, 10, 15, 30 minutes, 1, 2, 3, 5, 7, 12, 24, and 48 hours post-dose for the single-dose study. For the multiple-dose study, blood samples (5 mL) were collected prior to dosing on days 1, 5, 6, and 7 (0 hours prior to dosing) and 2, 5, 10, 15, 30 minutes, 1, 2, 3, 5, 7, 9, 12, 15, 24, and 36 hours post-dose on day 1 and day 7. Plasma was separated and stored at -20°C for analysis.

Urine samples were collected at 0 hours (pre-dose), 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36, and 36–48 hours post-dose for the single-dose study. The total volume of urine in each time interval was recorded and stored at -20°C for analysis.

Safety Monitoring

Throughout the study, all subjects remained in the study unit under continuous observation. Details of adverse events (AEs) were obtained and recorded by the study physicians. Routine safety and tolerability were evaluated through AE reporting by the investigators and subjects, on the basis of vital signs, physical examination, laboratory examination (routine blood, urine and feces test, occult blood test and blood biochemical test) and ECG, which were performed at scheduled intervals during the studies. AEs that occurred during the study were classified as mild (awareness of a sign or symptom but comfortably tolerated), moderate (discomfort that may interfere with daily activities) or serious (death, life-threatening, requiring hospitalization or incapacitating). AEs were recorded and reported according to GCP.

Pharmacokinetic Measurement

The concentrations of BCQB in plasma and urine were determined by validated liquid chromatography-mass spectrometry methods.^[20,21] The lower limit of quantitation (LLOQ) of BCQB in plasma was 5 pg/mL, while in urine it was 0.02 ng/mL. The pharmacokinetic parameters were calculated by WinNonlin Professional software (Version 6.1, Pharsight Corporation, Mountain View, CA, USA) using non-compartmental methods. The pharmacokinetic parameters in these studies were maximum plasma concentration (C_{max}), the time to C_{max} (t_{max}), the minimum value of the steady-state plasma drug concentration ($C_{min,ss}$), elimination half-life ($t_{1/2}$), the area under the plasma concentration-time curve (AUC) from time 0 to time t (AUC_t), the AUC from time 0 to infinity (AUC_{∞}), the steady-state AUC (AUC_{ss}), apparent clearance (CL/F), apparent total volume of distribution (V_d/F), the average steady-state concentration (C_{av}), the degree of fluctuation (DF), the accumulation ratio (R_{ac})

and the percentage of BCQB dose recovered in urine ($f_e\%$).

Statistical Analysis

Statistical analysis was performed using SPSS software version 11.0 (SPSS, Inc., Chicago, IL, USA). Prior to analysis, dose-dependent parameters (C_{\max} and AUC) were determined using natural logarithms of individual values. For the exploration of dose proportionality, the slope β and 90% confidence intervals (CIs) obtained from the power model: $\ln(\text{AUC or } C_{\max}) = \alpha + \beta \times \ln(\text{dose})$ were computed by analysis of covariance (ANCOVA). The regression coefficient was significant at level 0.1. The pre-defined criterion was set as (0.500, 2.000),^[22] and the criterion interval resulted in the value of (0.500, 1.500). The differences in pharmacokinetic parameters among dose groups were compared using ANOVA except for t_{\max} for which the non-parametric test (NPT) was used. Statistical comparisons between pharmacokinetic parameters of single and multiple doses were performed by the paired t-test (PTT), and the differences of pharmacokinetic parameters between male and female subjects were compared by the independent t-test (ITT). To determine whether steady state was reached in the multiple-dose study, the differences in $C_{\min,ss}$ on days 5, 6, and 7 were compared using ANOVA.

Results

Study Population

Healthy males and females ($n=98$) participated in the FIH studies. No subject dropped out of the study. Baseline demographics of the study population are presented in table I.

Single-Dose Pharmacokinetic Study

The mean plasma concentration-time curves are shown in figure 2, and the main pharmacokinetic parameters of BCQB are presented in table III. Absorption of BCQB after intranasal administration was rapid, with a median t_{\max} of 8 minutes for 45, 90, and 180 μg doses, and the plasma concentrations of BCQB decreased in a

biphasic manner, with the mean $t_{1/2}$ of 8.5 hours across the doses.

The mean and SD values of C_{\max} , AUC_t and AUC_∞ versus dose relationships after single intranasal dosing of BCQB are presented in figure 3. Over the dose range studied, the mean C_{\max} , AUC_t and AUC_∞ increased linearly across the doses by linear regression analysis, with regression equations in figure 3. Dose proportionality was observed ($p > 0.05$) by the ANOVA on the values of $\ln(C_{\max}/\text{dose})$ and $\ln(\text{AUC}/\text{dose})$ among the three dose groups. Moreover, the mean slopes of the plots for $\ln(C_{\max})$ or $\ln(\text{AUC})$ versus $\ln(\text{dose})$ were all close to 1, and the 90% CIs of the slopes were completely contained within the predefined range (0.500, 1.500) for dose proportionality. The mean slopes (90% CIs) were 1.067 (0.834, 1.300) for C_{\max} , 1.207 (0.921, 1.494) for AUC_t , and 1.051 (0.762, 1.341) for AUC_∞ . Thus, C_{\max} and AUC proved to be dose proportional across the studied doses by different methods. The values of t_{\max} , $t_{1/2}$, CL/F and $f_e\%$ were independent of dose ($p > 0.05$). There was no clinically significant pharmacokinetic difference ($p > 0.05$, by ITT) between males and females in the single-dose study.

Multiple-Dose Pharmacokinetic Study

The mean plasma concentration-time curves of BCQB after the first dose (day 1) and the last dose (day 7) are presented in figure 4, and the pharmacokinetic parameters from the non-compartmental analysis of measured plasma concentrations on day 1 and day 7 are provided in table IV.

No significant difference in $C_{\min,ss}$ was found by ANOVA analysis, indicating that steady-state conditions were achieved by day 5 after two consecutive three times daily 120 μg doses of BCQB. Under steady-state conditions, BCQB was rapidly absorbed with the median t_{\max} of 8 minutes and a mean C_{\max} of 158.3 pg/mL , which were identical to the single-dose parameters (day 1). BCQB cleared from plasma in a biphasic manner with no significant difference of $t_{1/2}$ between the first and the last dose. However, the mean AUC values were higher in the multiple-dosing regimen than the corresponding values obtained after single-dose (day 1) administration ($p < 0.01$), and slight

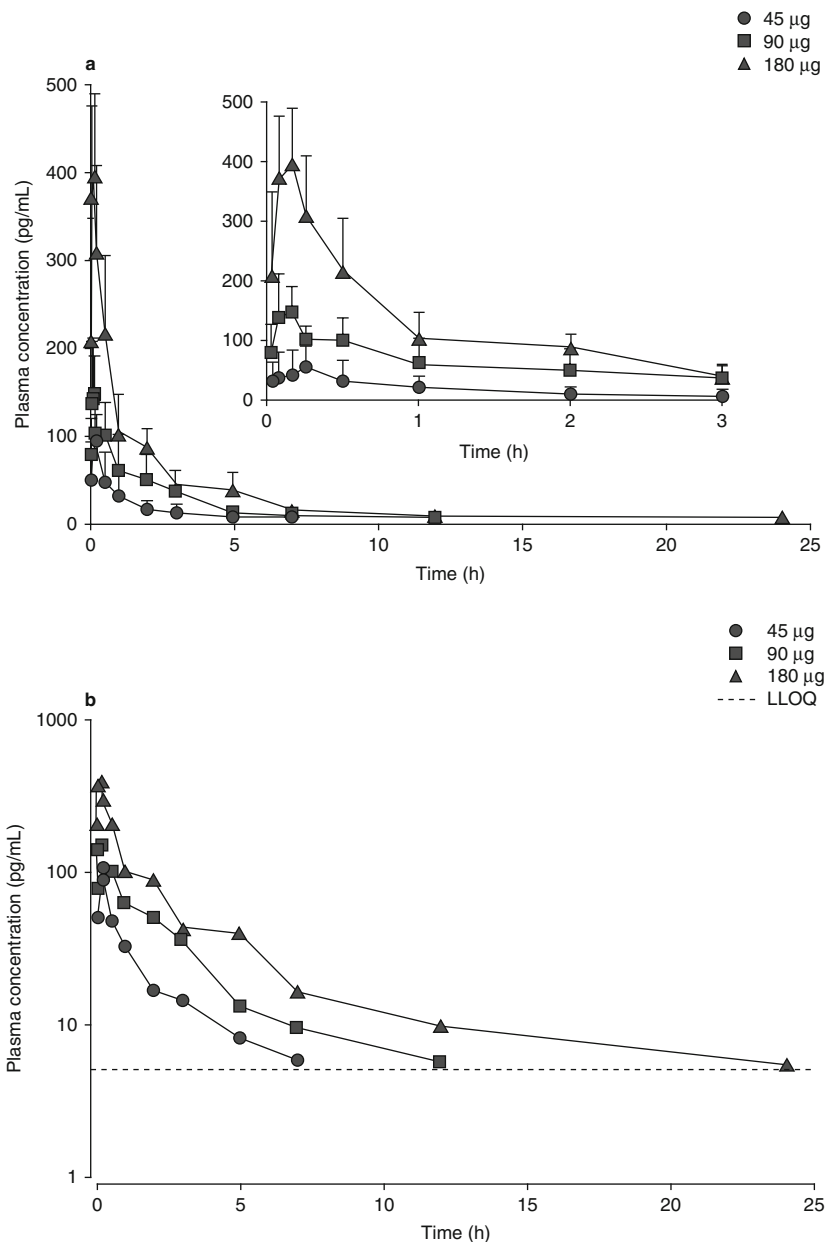


Fig. 2. Mean plasma (a) and log-scaled mean plasma (b) concentration-time profiles of bencycloquidium bromide following single intranasal doses in healthy Chinese subjects. The inset expands the first 3 hours of the profile. Data are presented as mean + SD ($n = 10$ per dose). LLOQ = lower limit of quantitation.

accumulation was found following repeat dosing of BCQB with R_{ac} of 1.26 for AUC_{τ} ($\tau = 5$ hours). A high DF of BCQB in plasma was achieved at

2.7 ($\tau = 5$ hours). Sex difference had no significant influence on AUC, C_{max} , t_{max} , and $t_{1/2}$ between the first and the last dose.

Table III. Main pharmacokinetic parameters of bencycloquidium bromide in healthy Chinese subjects after single intranasal doses 45, 90, and 180 μg^{a}

Parameters	Dose (μg)		
	45 (n=10)	90 (n=10)	180 (n=10)
C_{max} (pg/mL)	110.4 \pm 52.5	170.6 \pm 63.4	432.1 \pm 93.9
t_{max} (min)	8 (2–15)	8 (5–30)	8 (5–15)
$t_{1/2}$ (h)	7.4 \pm 5.5	7.5 \pm 6.8	10.7 \pm 5.3
AUC_t (ng \cdot h/L)	159.5 \pm 104.6	338.6 \pm 174.6	743.0 \pm 264.0
AUC_{∞} (ng \cdot h/L)	218.6 \pm 137.6	415.7 \pm 258.2	831.3 \pm 291.4
CL/F (L/h)	298.3 \pm 228.3	285.8 \pm 139.1	243.8 \pm 90.2
Vd/F (L)	2218 \pm 863	2161 \pm 1097	3438 \pm 1202
$f_e\%$	4.5 \pm 2.3	4.6 \pm 2.1	3.6 \pm 1.6

^a Data are presented as mean \pm SD except for t_{max} , which was expressed as median (range).

AUC_{∞} =area under the concentration-time curve from time 0 to infinity; AUC_t =AUC from time 0 to time t ; CL/F=apparent total body clearance; C_{max} =maximum concentration; $f_e\%$ =the cumulative percentage of bencycloquidium bromide excreted in urine; $t_{1/2}$ =half-life; t_{max} =time to C_{max} ; Vd/F=apparent volume of distribution.

Safety and Tolerability

BCQB was safe and well tolerated when administered as a single dose up to 450 μg and multiple doses up to 150 μg three times daily (450 $\mu\text{g}/\text{day}$) for 15 days. No death or serious adverse events (SAEs) were reported during the study and all subjects were in good compliance. No notable mean change from baseline was recorded in the vital signs or clinical laboratory variables. No individual participant value outside the laboratory reference ranges was considered to be clinically significant, and no clinically significant change in ECG and heart rate was reported in any participant during the study.

Most subjects reported one or more AE. AEs that occurred in two or more subjects, classified according to the Medical Dictionary for Regulatory Activities system organ class and preferred terms, are listed in table V. The most frequently reported AEs were nasal irritation (including nasal congestion, nasal dryness, redness of nasal mucosa, and epistaxis) and mydriasis. However, the nasal irritation was mild, of limited duration and no inflammation was seen on early or follow-up nasal examinations, while mydriasis was also mild, of limited duration and of no clinical significance. Overall, all the AEs reported were mild

in intensity, expected, based on the known activity of the drug or the intranasal route of administration, and not considered to be clinically significant. There was no trend for increasing AEs with increasing doses over the dose range evaluated.

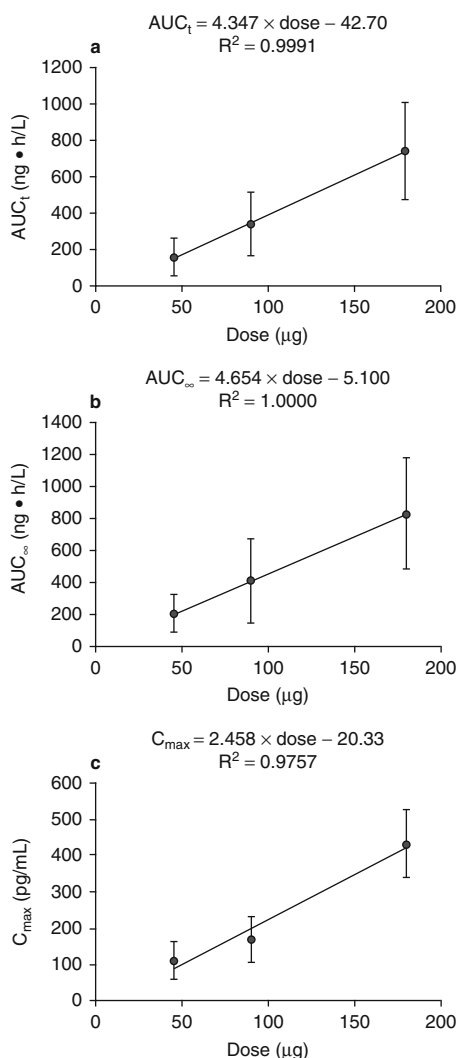


Fig. 3. Mean value (\pm SD) dose profiles of bencycloquidium bromide (BCQB) following single intranasal doses of BCQB 45, 90, and 180 μg (n=10 per dose). (a) AUC_t ; (b) AUC_{∞} ; (c) C_{max} . Linear regression is shown in the figure. AUC_t =AUC from time 0 to time t ; AUC_{∞} =AUC from time 0 to infinity; C_{max} =maximum concentration.

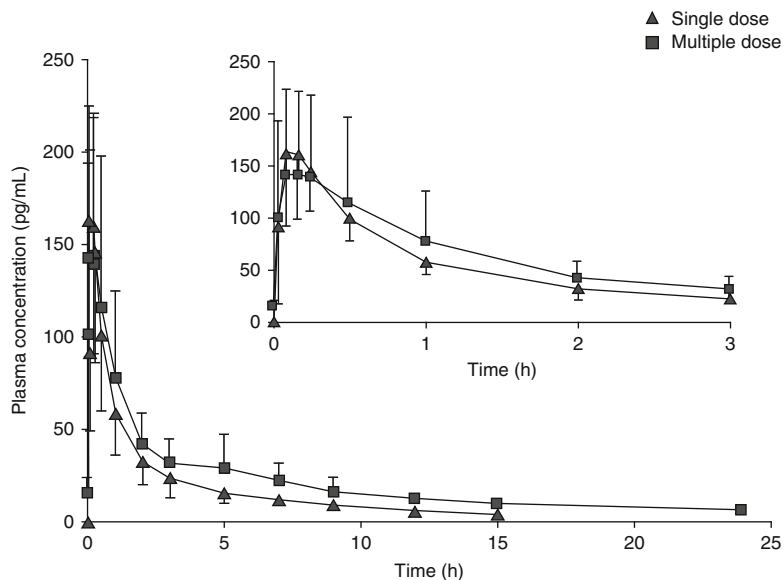


Fig. 4. Mean plasma concentration-time profiles of bencycloquidium bromide on day 1 and day 7 following multiple intranasal doses in healthy Chinese subjects, respectively. The inset expands the first 3 hours of the profile. Data are presented as mean \pm SD (n = 10 per dose).

Discussion

At present, the anticholinergic medications used in the treatment of airway diseases are not selective for muscarinic receptor subtypes.^[23] The novel selective muscarinic M1/M3 receptor antagonists, such as acclidinium bromide^[24] and penehyclidine hydrochloride,^[25,26] are under development for the therapy of chronic obstructive pulmonary disease (COPD), while the novel agents under development for the treatment of rhinorrhea in rhinitis are limited. BCQB is under development not only for the treatment of rhinorrhea in rhinitis but also for the therapy of COPD.^[7,11] The aerosol with quantitative inhalation of bencycloquidium bromide^[27] is under development.

The objective of this FIH study was to assess the pharmacokinetics, safety and tolerability after single and multiple intranasal doses of BCQB in healthy Chinese subjects. Following single intranasal doses in healthy Chinese adult subjects, BCQB was rapidly absorbed, the plasma concentration of BCQB decreased in a biphasic manner, the C_{max} and AUC of BCQB increased in proportion to the studied doses, and the mean $t_{1/2}$ and the mean CL/F were independent of the

administered doses. The mean $t_{1/2}$ of the studied dose groups ranged from 7.4 to 10.7 hours. The small difference of $t_{1/2}$ observed was due to assay

Table IV. Main pharmacokinetic parameters of bencycloquidium bromide in healthy Chinese subjects after multiple intranasal administration of 120 μ g, with single administration on day 1; received no treatment on day 2; and continued to receive the study drug three times daily from days 3 through 7^a

Parameters	Day 1 120 μ g (n = 10)	Day 7 120 μ g (n = 10)
AUC _t (ng • h/L)	334.9 \pm 127.0	551.4 \pm 255.4
AUC _{∞} (ng • h/L)	430.0 \pm 183.6	662.2 \pm 278.7
t_{max} (min)	8 (2, 30)	8 (2, 30)
$t_{1/2}$ (h)	11.0 \pm 9.5	12.3 \pm 4.2
C_{max} (pg/mL)	175.4 \pm 77.2	158.3 \pm 77.8
$C_{ss,min}$ (pg/mL)		16.12 \pm 8.49
C_{av} (pg/mL)		63.76 \pm 24.78
DF		2.7 \pm 0.9
R_{ac}		1.26 \pm 0.39

a Data are presented as mean \pm SD except for t_{max} , which was expressed as median (range).

AUC_t = area under the concentration-time curve from time 0 to time t; **AUC _{∞}** = AUC from time 0 to infinity; **C_{av}** = the average steady-state concentration; **C_{max}** = maximum concentration; **$C_{ss,min}$** = the minimum value of the steady-state plasma drug concentration; **DF** = the degree of fluctuation; **R_{ac}** = the accumulation ratio; **$t_{1/2}$** = half-life; **t_{max}** = time to C_{max} .

Table V. Treatment-emergent adverse events occurring in two or more subjects (safety population, n=58)

Treatment-emergent adverse events	Safety assessment									
	Single dose (μg)							Multiple doses (μg)		
	45	90	180	270	360	450	Total	120	150	Total
n	6	8	8	8	6	6	42	8	8	16
Upper respiratory										
Nasal dryness	4	2	0	2	0	4	12	5	3	8
Nasal congestion	4	3	3	0	4	1	15	6	4	10
Epistaxis	2	0	0	0	0	0	2	1	0	1
Color of nasal mucosa (red)	3	1	3	0	0	0	7	0	0	0
Color of nasal mucosa (pale)	0	0	0	1	0	1	2	0	0	0
Other nasal symptoms	0	0	0	0	0	3	3	1	0	1
Neurology										
Headache	1	0	0	0	0	0	1	1	0	1
Dizziness	2	1	0	0	0	0	3	0	0	0
Drowsiness	0	0	0	0	0	0	0	2	0	2
Ocular										
Ocular hypertension	0	0	1	0	0	0	1	1	0	1
Mydriasis	0	2	1	1	3	1	8	5	4	9
Gastrointestinal										
Dry mouth	0	0	0	2	0	0	2	0	0	0

limitations in the determination of the BCQB concentration in the terminal phase of the concentration-time curve, where plasma concentrations of BCQB at sampling times in the latter part of the concentration-time curve were below the LLOQ (5 pg/mL) for many subjects, particularly at lower doses (figure 2). However, no statistical significance ($p > 0.05$) in $t_{1/2}$ was found among the studied dose groups. The duration of action of 50% of BCQB ($t_{1/2}$, off-set) in classical bioassays was approximately 3 hours,^[11] which was shorter than the terminal $t_{1/2}$ of BCQB in plasma. It may be due to the fact that the terminal $t_{1/2}$ in plasma is reflective of the rate of drug elimination from the body but not reflective of the duration of drug action.

In the multiple-dose study, the steady-state concentration was achieved within 3 days of consecutive dosing and the pharmacokinetic parameters of BCQB were similar to those following single dose except AUC. A slight accumulation was noted with the mean R_{ac} of 1.26 based on AUC_{τ} , but the slight accumulation resulted in sustained plasma exposure upon daily dosing. A high DF for BCQB concentration in plasma was ob-

served, for the concentrations of BCQB in plasma declined rapidly from t_{max} to τ .

Wide inter-subject variability in pharmacokinetic parameters was reflected in their SD (tables III and IV), but the reasons were not clear. There are several factors that can lead to the variability of pharmacokinetic parameters. First, although physicians administered BCQB carefully according to the SOPs, the intranasal administration process may cause variability. For example, while intranasal doses were administered to the lateral nasal wall, the influence of factors (such as posture, position of the head, and nasal mucosal blood flow) could increase the variability of pharmacokinetic parameters. Second, the presence of nasal mucosal physiology and pathology is another potential source of variability.^[28] For example, hyperemia would be expected to influence drug absorption after intranasal application, for the hyperemia can change the penetration of nasal mucosa, which may influence drug absorption. Third, only ten subjects had been studied for the pharmacokinetic profile in each group and the variability in one or more individual would affect

the overall results greatly. Future clinical studies should also seek to identify the factors responsible for variability in intranasal dose delivery, deposition and mucosa absorption in order to optimize the safety profile of BCQB that could often be required for long-term therapy.

In this FIH study, repeated administration of BCQB did not lead to any cardiovascular adverse event in healthy subjects, consistent with previously published results in animals.^[13,14] However, future investigations to evaluate the effect of long-term doses of BCQB on the nasal mucosa, ECG and heart rate are warranted.

Conclusion

BCQB was safe and well tolerated in this FIH study. No SAEs occurred, no change of ECG and heart rate was observed, and all subjects were in good compliance. The mean C_{max} and AUC of BCQB were proportional to the studied doses, and the steady state was achieved within 3 days. A slight accumulation following 5 days of 120 µg three times daily dosing of BCQB was observed, but the elimination rate showed no change. On the basis of this study in healthy subjects, BCQB is worthy of further investigation for treating rhinorrhea in rhinitis.

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