Safety, tolerability, and pharmacokinetics of a single ascending dose of baicalein chewable tablets in healthy subjects

Min Li, Aixin Shi, Hongxian Pang, Wei Xue, Yang Li, Guoying Cao, Bei Yan, Fan Dong, Kexin Li, Wei Xia, Guorong He, Guanhua Du, Xin Hu

* Beijing Key Laboratory of Drug Clinical Risk and Personalized Medication Evaluation, Department of Clinical pharmacology, Beijing Hospital of the Ministry of Health, Beijing 100730, China
\* StateKey Laboratory of New-tech for Chinese Medicine Pharmaceutical Process, JiangsuKanion Pharmaceutical Co. LTD., Lianyungang, Jiangsu 222001, China
\* Beijing Key Laboratory of Drug Targets Identification and Drug Screening, Institute of Materia Medica, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100050, China

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A B S T R A C T

Ethnopharmacological relevance: The root of Scutellaria baicalensis Georgi has been used extensively in traditional Chinese medicine for the treatment of inflammation, fever, cough, dysentery, and hypertension. Baicalein is a flavonoid isolated from the root of Scutellaria baicalensis Georgi and is a novel neuroprotective agent under development for the treatment of Parkinson's disease. We aimed to investigate the pharmacokinetic (PK) properties of baicalein and its main metabolite, baicalin, after single-dose administration in healthy Chinese subjects. The safety and tolerability of baicalein were also assessed.

Materials and methods: This was a Phase I, randomized, double-blind, single-dose trial of baicalein (100–2800 mg) in 72 healthy adults. Samples of blood, urine and feces were collected at regular intervals up to 48 h after administration of the study drug. Baicalein and baicalin were then analyzed using liquid chromatography-tandem mass spectrometry (LC/MS/MS). The maximum concentration that the drug achieved after dosing (C\text{max}), time to C\text{max} (t\text{max}), terminal half-life (t\text{1/2}), area under the curve from time zero to time of last quantifiable concentration (AUC\text{0–t}), area under the curve from time zero to infinity (AUC\text{0–\infty}), apparent total plasma clearance (CL/F), and apparent total volume of distribution (V/F) were determined using non-compartmental models. Dose proportion was tested using a method combining the equivalence criterion and power model. Physical examinations, vital signs, ECG findings, hematology, and urinalysis were monitored before and at regular intervals after administration of the study drug.

Results: The PK profile of baicalein and baicalin was characterized by a median t\text{max} of 0.75–3.5 h and 0.5–3 h, respectively, followed by a multiphasic profile with a t\text{1/2} of 1.90–15.01 h and 4.22–10.80 h, respectively. The estimates of the proportionality coefficient (90% CI) for C\text{max}, AUC\text{0–t}, and AUC\text{0–\infty} were 0.83 (0.70–0.96), 0.91 (0.81–1.00) and 0.92 (0.82–1.02), respectively. All values overlapped within the pre-specified range of (0.89–1.11), (0.93–1.07), and (0.93–1.07), respectively. Dose proportionality was inconclusive for a baicalein dose range of 100–2800 mg. The total urinary clearance of baicalein and baicalin was < 1%. Approximately 27% of baicalein was eliminated as unchanged drug in feces. Baicalein was well tolerated. Eleven treatment-related adverse events were observed, and all were rated as "mild" and resolved without further treatment. No serious adverse events occurred.

Conclusions: Single oral doses of 100–2800 mg of baicalein were safe and well tolerated by healthy subjects. Clinical laboratory assessments showed no signs of toxicity in the liver or kidney. The favorable safety profile and PK properties warrant further clinical studies for baicalein.

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1. Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disorder caused by the disturbance of the function of the extrapyramidal system. The prevalence of PD in people aged > 60 years is ~ 1% (Nutt and Wooten, 2005). The precise pathogenesis of PD is not known, but environmental factors, genetic factors,
inflammatory responses, oxidative stress, and mitochondrial dysfunction might be involved in the development of PD (Dauer and Przedborski, 2003; Von Bohlen und Halbach et al., 2004; Niranjan, 2013). Several drugs have been developed for the treatment of PD, but one that can retard the progression of PD has not been identified (Koller and Tse, 2004; Pedrosa and Timmermann, 2013). Moreover, the long-term utility of these drugs (e.g., levodopa) are often limited by their unavoidable side effects. New drugs with novel mechanisms and fewer side effects are needed urgently. Recently, the concept of “neuroprotective therapy” has emerged as a potential treatment of PD (Olanow and Jankovic, 2005; Hart et al., 2009).

“Skullcap”, the root of Scutellaria baicalensis Georgi, has been used extensively in traditional Chinese medicine for the treatment of inflammation, fever, cough, dysentery, and hypertension (Lin and Shieh, 1996). More than 50 compounds have been isolated and identified from skullcap. Flavonoids are the principal components contributing to its bioactivity (Gao et al., 1999).

Baicalein (5,6,7-trihydroxyflavone) is a flavonoid originally isolated from skullcap (Fig. 1). Among its multiple biological activities, anti-oxidant, anti-inflammatory and neuroprotective activities have been demonstrated in various in vitro and in vivo models (Shao et al., 2002; Shen et al., 2003). Studies have demonstrated that baicalein exerts neuroprotective effects in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- and 6-hydroxydopamine-induced experimental models of PD (Lee et al., 2005; Cheng et al., 2008; Mu et al., 2009). Studies on molecular mechanisms have suggested that baicalein exerts its neuroprotective effects by regulating the function of the dopaminergic system and anti-oxidative damage. The anti-inflammatory effects and improved mitochondrial dysfunction of baicalein have also been observed (Mu et al., 2011; Li et al., 2012). Those results suggest that baicalein could have multiple mechanisms of actions on Parkinson’s disease (Yu et al., 2012). An application for a clinical trial using baicalein to treat PD has been approved by the China Food and Drug Administration.

The primary objective of our study was to investigate the pharmacokinetic (PK) properties of baicalein and its primary metabolite baicalin after administration of single escalating oral doses. The secondary objective was to characterize the safety and tolerability of baicalein in healthy male and female Chinese volunteers.

2. Methods

2.1. Study design

This trial was a single-center, randomized, double-blind, placebo-controlled, single dose-escalation Phase I study with healthy males and females. Research was conducted in accordance with Good Clinical Practice procedures and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of the Beijing Hospital of the Ministry of Health (Beijing, China). Written informed consent was obtained from each subject before commencement of any protocol-specific procedures and after full explanation of the study design.

The dose started at 100 mg, then escalated to 200, 400, 800, 1200, 1600, 2200, and 2800 mg. Six participants received 100 mg of β-form baicalein in the preliminary study. Then, treatment allocation was undertaken in sequential groups of 8–10 participants per dose group. Among the 8–10 subjects within each group, 2 subjects were assigned randomly to receive the placebo and 6–8 assigned randomly to receive the β-form active drug. Evaluations (safety, PK) were conducted before escalation to the next dose level. Chewable doses were administered with 200 mL of water after an overnight fast of ≥ 10 h and standardized meals were started 4 h after dosing.

2.2. Subjects

The study population comprised healthy male and female subjects (18–40 years; body mass index (BMI), 19–25 kg/m²). Exclusion criteria were clinically significant abnormal medical history or physical examination; excessive alcohol intake or smoking; participation in any other clinical trial < 4 weeks before the first dose or consumption of any prescription/over-the-counter drug < 2 weeks before administration; aiming to becoming pregnant in < 6 months. Laboratory tests, vital signs and cardiac parameters (electrocardiography (ECG)) had to be within normal parameters. Subjects had to refrain from consumption of alcohol, cigarettes, brassicaceous vegetables, tomato, soya, apples, oranges or grapefruits for 3 days before dosing and during hospital admission.

2.3. Investigational products

Baicalein chewable tablets and placebo were manufactured in accordance with applicable GMP and complying with applicable regulatory requirements. Batch sample analyses and characteristics records were maintained. The active ingredient was β-form baicalein. The inactive ingredients included mannitol, microcrystalline cellulose, aspartame, citric acid, sodium hydrogen sulfite, sodium calcium edentate, and other ingredients.

2.4. Safety evaluation

Safety assessments comprised recording of all adverse events (AEs) and serious adverse events (SAEs) along with their severities and their relationship to the study drug. Safety assessments also included regular monitoring by: hematology; analyses of serum chemistry; coagulation assays; urinalysis; determination of vital signs; 12-lead ECG; physical examinations. The medications that the subjects were taking concomitantly were noted. Safety and tolerability results were analyzed descriptively.
2.5. Sampling of plasma, urine and feces

2.5.1. Plasma collection

A series of time points was chosen at which to collect the blood samples of subjects over a period of 48 h after dosing. Samples were obtained at time zero (pre-dosing) 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 h for the preliminary study (100 mg); and at time zero (pre-dosing), 10, 20, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 h for the remainder of the groups (200–2800 mg). At each time for each subject, 3 mL of blood was collected. The blood sample was centrifuged at 1811 g for 10 min at 4 °C within 30 min of collection. Plasma was divided into 3 parts and transferred to centrifuge tubes containing Vitamin C (10 mg mL⁻¹) as a stabilizer. These tubes were labeled and stored at −70 °C for subsequent analyses.

2.5.2. Urine collection

Blank urine samples were collected at −2 h to 0 h (pre-dosing). Subsequently, urine samples were collected over six intervals (0–4, 4–8, 8–12, 12–24, 24–36, and 36–48 h) after administration of the study drug. Urine samples were collected at each time point, mixed well with the stabilizer Vc (10 mg mL⁻¹) and volumes measured accurately. 10 mL of each sample was retained in a test tube, divided into three parts, sealed immediately, and stored at −70 °C for subsequent analyses.

2.5.3. Feces collection

Blank feces samples were collected at −12 h to 0 h (pre-dosing). Subsequently, feces samples (if any) were collected over a period of 48 h after dosing. Feces samples were weighed, homogenized with an aqueous solution of 0.1% formic acid, and the volume measured accurately. 10 mL of each sample was retained in a test tube, divided into three parts, mixed with the stabilizer Vc (10 mg mL⁻¹), sealed immediately, and stored at −70 °C for subsequent analyses.

2.6. Bioanalytical methods

Samples of plasma, urine and feces were analyzed for concentrations of baicalein and baicalin. Briefly, liquid–liquid extraction was employed for pretreatment of plasma and urine samples, and a protein precipitation method was used for pretreatment of feces samples. Chromatographic separation was undertaken using a C12 column with gradient elution. That is, A: acetonitrile–methanol (50:50, v/v) solution containing 0.5% formic acid; and B: aqueous solution of 3 mM ammonium acetate containing 0.5% formic acid. The gradient flow rate was 0.30 mL min⁻¹ and the entire analysis lasted for 12 min. Concentrations of baicalein and baicalin were measured using a triple quadrupole tandem mass spectrometer in multiple reaction monitoring (MRM) mode via a positive electrospray ionization source. The m/z ratios of monitored parent ions and daughter ions of baicalein were 271.1 and 271.0 for baicalin in plasma and feces, whereas 447.1 and 271.0 were monitored for baicalin in urine. The calibration range in plasma samples was 2.7. Statistical analyses

The PK parameters were the maximum concentration that the drug achieved after dosing (Cmax); time to Cmax (Tmax); terminal half-life (T1/2); area under the curve from time zero to time of last quantifiable concentration (AUC0–∞); area under the curve from time zero to infinity (AUC0–∞); apparent total plasma clearance (CL/F); and the apparent total volume of distribution (V/F). These parameters were derived by non-compartmental analysis using WinNonlin® v6.1 (Pharsight, St Louis, MO, USA) and summarized as the mean ± SD. Dose proportionality was assessed using a method combining the equivalence criterion and power model (Gough et al., 1995; Smith et al., 2000).

3. Results

3.1. Subjects

Seventy-two healthy male (n=46) and female (n=26) volunteers (mean age, 29.2 (range, 21–39) years; mean weight, 62.2 (range, 50–80) kg) were enrolled. Two subjects discontinued before drug administration: one because of high blood pressure and the other because of an ECG abnormality. Another subject withdrew 24 h after drug administration because of fear of blood sampling. All 70 subjects who were administered with baicalein were included in the pharmacokinetic analysis.

3.2. Safety

There were 34 AEs in 24 subjects after administration of the study drug or placebo. All AEs were rated as “mild” and resolved without further treatment. Of the 34 reported AEs, 11 were determined by the study investigators to be probably or possibly related to the study drug (Table 1). The overall prevalence of AEs was the highest in the 1600-mg group (6/10 subjects, 60%) and ranged from 0% to 50% in the other groups. There was no evidence of a dose-related increase in AEs with baicalein administration. There were no SAEs in this study. None of the subjects withdrew from the study or were discontinued by the investigators because of AEs. There were no clinically relevant changes in blood pressure or ECG in individuals during the study.

3.3. PK

The mean plasma concentration–time curves of baicalein and its metabolite baicalin after drug administration are shown in Fig. 2. The PK parameters derived by non-compartmental analysis of baicalein and baicalin are shown in Tables 2 and 3.

The mean plasma concentration–time profiles of baicalein administration were characterized by a median Tmax that varied from 0.75 h to 3.5 h across the dose groups, with mean Cmax values ranging from 0.75 h to 3.5 h across the dose groups, with mean Cmax values
ranging from 5.82 ng mL\(^{-1}\) (100 mg) to 108.17 ng mL\(^{-1}\) (2800 mg). The mean \(t_{1/2}\) of baicalein varied from 1.9 h to 15.01 h.

The shape of the plasma concentration–time profiles for baicalein resembled that of the parent compound: it had multiple peaks. The median \(t_{1/2}\) varied from 0.5 h to 3.0 h across the dose groups. The mean \(t_{1/2}\) varied from 4.22 h to 9.65 h. However, exposure to the metabolite baicalein was much higher compared with baicalein, with mean \(C_{\text{max}}\) values ranging from 75.47 ng mL\(^{-1}\) (100 mg) to 2264.50 ng mL\(^{-1}\) (2200 mg).

The dose proportionality constant, \(\beta\) for baicalein was 0.83 (90% confidence interval (90% CI), 0.70–0.96), 0.91 (0.81–1.00), and 0.92 (0.82–1.02), for \(C_{\text{max}},\) AUC\((0-\infty)\), and AUC\((0-\tau)\), respectively. These values overlapped with the acceptance interval (0.89–1.11), (0.93–1.07), and (0.93–1.07), for \(C_{\text{max}},\) AUC\((0-\tau)\), and AUC\((0-\infty)\), respectively, suggesting that dose proportionality of baicalein for \(C_{\text{max}},\) AUC\((0-\tau)\), and AUC\((0-\infty)\) was inconclusive.

The dose proportionality constant, \(\beta\) for baicalin was 0.82 (90% confidence interval (90% CI), 0.69–0.95), 0.89 (0.78–1.00) and 0.88 (0.78–0.99) for \(C_{\text{max}},\) AUC\((0-\tau)\), and AUC\((0-\infty)\), respectively. These values overlapped within the pre-specified range, suggesting that dose proportionality of baicalin for \(C_{\text{max}},\) AUC\((0-\tau)\), and AUC\((0-\infty)\) was also inconclusive.

The amount of drug excreted in urine from 0 h to 48 h after dosing was 0.20–4.51 mg of baicalein at a dose range of 100–2800 mg, which corresponded to 0.10–0.27% of the administered dose, respectively. The amount of baicalein excreted in feces from 0 h to 48 h after dosing was 7.72–898.13 mg at a dose range of 100–2800 mg, which corresponded to 7.72% and 40.82% of the administered dose, respectively (Table 2).

The amount excreted in urine from 0 h to 48 h after dosing was 1.32 mg to 22.76 mg of baicalin at a dose range of 100 mg to 2800 mg, respectively. The amount of baicalein excreted in feces from 0 h to 48 h after dosing ranged between 0.01 mg and 36.43 mg at a dose range of 100 mg to 2800 mg, respectively (Table 3).

4. Discussion

The present first-in-human study was designed to investigate the PK, safety and tolerability of baicalein after oral administration in healthy subjects of both sexes.

Previous studies have demonstrated that baicalein has two crystal forms, \(\alpha\)-form and \(\beta\)-form. The crystalline pattern of naturally occurred baicalein was \(\alpha\)-form with very low bioavailability, which was described in many studies. Therefore, therapeutically applications of naturally occurred baicalein were limited by its low bioavailability. On the other hand, the bioavailability of the newfound \(\beta\)-form was much higher than the \(\alpha\)-form, which could achieve therapeutic concentrations in various animal models. For example, the absolute bioavailability of \(\beta\)-form in monkeys ranged from 13% to 23% at 50–500 mg/kg dose level (Tian et al., 2012). The application for the patent of two crystal substances of baicalein, and preparations, pharmaceutical composition and uses thereof has been granted (CN101434593 B, Du et al., 2013). The \(\beta\)-form baicalein used in the present study was expected to achieve higher body exposure in man compared with naturally occurred \(\alpha\)-form.

The single-ascending-dose design permitted the safety and PK data at a lower dose to be evaluated before proceeding to higher doses. Preclinical toxicology data fully supported the safety of the starting dose. Using the standardized algorithm recommended by FDA (Food and Drug Administration, 2005), 1200-mg was the upper limit of starting doses (12-fold for the 100-mg starting dose we used). Eight single dose levels were investigated from 100 mg to 2800 mg, resulting in a maximum 28-fold increase in dose.

The plasma concentration–time profiles of baicalein showed that maximum plasma concentrations were achieved \(\approx 0.75\) h to \(\approx 3\) h after administration and, thereafter, baicalein concentrations decreased in a multiphasic way. The multiple peaks of baicalein in the plasma drug concentration–time profile observed in the present study and the predominant amount of baicalein compared

![Fig. 2. Mean plasma concentration vs. time profiles of baicalein (A) and its metabolites baicalin (B) after a single dose (n=6–8 per group) of 100–2800 mg baicalein.](image)

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100 mg</th>
<th>200 mg</th>
<th>400 mg</th>
<th>800 mg</th>
<th>1200 mg</th>
<th>1600 mg</th>
<th>2200 mg</th>
<th>2800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(t_{1/2}) (h)</td>
<td>1.90 (1.17)</td>
<td>8.03 (3.07)</td>
<td>4.82 (2.95)</td>
<td>8.23 (1.84)</td>
<td>10.16 (4.07)</td>
<td>8.71 (2.00)</td>
<td>7.29 (4.16)</td>
<td>15.01 (14.97)</td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td>3.5 (0.5–5)</td>
<td>3 (0.5–5)</td>
<td>3 (0.17–5)</td>
<td>1.5 (0.17–4)</td>
<td>2 (0.17–5)</td>
<td>1.5 (0.5–4)</td>
<td>1.25 (0.17–5)</td>
<td>0.75 (0.33–4)</td>
</tr>
<tr>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>5.82 (3.33)</td>
<td>11.54 (4.10)</td>
<td>20.47 (11.81)</td>
<td>35.38 (19.17)</td>
<td>51.62 (46.50)</td>
<td>43.06 (22.67)</td>
<td>131.36 (140.25)</td>
<td>108.17 (83.16)</td>
</tr>
<tr>
<td>AUC((0-\tau)) (ng/mL h)</td>
<td>21.90 (10.98)</td>
<td>69.15 (18.74)</td>
<td>98.25 (59.44)</td>
<td>210.57 (77.41)</td>
<td>307.91 (164.21)</td>
<td>239.18 (71.22)</td>
<td>478.45 (263.47)</td>
<td>540.93 (175.71)</td>
</tr>
<tr>
<td>AUC((0-\infty)) (ng/mL h)</td>
<td>24.95 (10.78)</td>
<td>74.94 (17.87)</td>
<td>101.72 (60.90)</td>
<td>218.02 (78.50)</td>
<td>323.48 (164.63)</td>
<td>255.23 (80.64)</td>
<td>497.45 (263.47)</td>
<td>678.23 (304.95)</td>
</tr>
<tr>
<td>(V_d/F) (L)</td>
<td>15,926 (18,345)</td>
<td>32,723 (13,955)</td>
<td>28,519 (15,465)</td>
<td>48,631 (18,968)</td>
<td>62,778 (50,138)</td>
<td>68,281 (45,724)</td>
<td>95,743 (45,724)</td>
<td>80,950 (47,692)</td>
</tr>
<tr>
<td>(C_{\text{LZ/F}}) (L/h)</td>
<td>4796 (2491)</td>
<td>2797 (536)</td>
<td>5072 (2384)</td>
<td>4078 (1393.46)</td>
<td>4438 (1824)</td>
<td>6892 (2387)</td>
<td>5398 (2396)</td>
<td>4029 (2153)</td>
</tr>
<tr>
<td>(U_{\text{Recoverd}}) (%)</td>
<td>0.20 (0.09)</td>
<td>0.25 (0.05)</td>
<td>0.19 (0.10)</td>
<td>0.15 (0.06)</td>
<td>0.13 (0.04)</td>
<td>0.10 (0.03)</td>
<td>0.16 (0.10)</td>
<td>0.16 (0.04)</td>
</tr>
<tr>
<td>(F_{\text{Recoverd}}) (%)</td>
<td>10.30 (13.70)</td>
<td>32.06 (22.04)</td>
<td>31.04 (16.84)</td>
<td>32.18 (28.65)</td>
<td>28.03 (20.20)</td>
<td>26.81 (18.97)</td>
<td>40.82 (36.97)</td>
<td>18.15 (17.76)</td>
</tr>
</tbody>
</table>
with its metabolite in feces are in accordance with the hypothesis that baicailein undergoes enterohepatic recirculation (Xing et al., 2005). This phenomenon has been reported to complicate absorption and recycling, and affect the PK of certain drugs by influencing \( t_{1/2} \), the area under the plasma concentration–time curve, and bioavailability (Tsai et al., 2000).

Studies have indicated that baicailein is well absorbed from the stomach and small intestine with limited absorption from the colon, whereas baicalin is moderately absorbed in the stomach but poorly absorbed from the small intestine and colon. These two moieties maintain a balance of systemic levels in the body through dynamic reconversion. However, it was concluded that baicailein was the preferred species for oral absorption because of a more rapid and complete absorption of baicailein and restoration of baicalin in the systemic circulation by the hydrolysis of baicailein. Circulating levels of baicalin would be expected to re-enter the gastrointestinal tract via biliary excretion (Taiming and Xueha, 2006).

In contrast to the relative low systemic levels of the parent compound baicailein, its most abundant metabolite conjugate, baicailein, was present in plasma at a \( C_{\text{max}} \) concentration range of 0.075–1.8 \( \mu \text{mol L}^{-1} \). The neuroprotective effect in rodent models is thought to be mediated primarily via the parent compound. The extensive glucuronidation and sulfation of baicailein with consequent poor bioavailability of the parent compound, as described here and previously, calls into question the role of the metabolite baicailein in the mediation of efficacy. The pharmacologic properties of most baicailein conjugates are not known, but baicailein (the 7β-glucuronidase-catalyzed conjugate) has been suggested to contribute to the pharmacologic activity of the parent molecule (Srinivas, 2010). In hepatoma cell lines, baicailein can induce apoptosis or inhibit proliferation (Chang et al., 2002). Baicailein also appears to retain (at least in part) the antioxidant properties of the parent molecule (Shieh et al., 2000). Therefore, the exposure of both baicailein and baicalin in the human body was studied.

Preclinical data showed that baicailein is metabolized predominantly by glucuronidation via uridine 5′-diphospho-glucuronosyltransferase systems. The urinary excretion of unchanged baicailein was extremely small. Of all the administered oral doses, \( \approx 0.7\% \) baicailein was excreted unchanged in urine and 27.1% excreted unchanged in feces within 48 h. These findings suggested that the drug might be excreted mainly in a metabolized form. The complete metabolic profile of baicailein in humans is still under investigation.

Enrolling female subjects early in the drug-development process is important for the assessment of sex-related differences in PK. The PK of baicailein after administration of a single dose was comparable in female and male subjects. Considering our small study cohort, however, data from more subjects will be required to confirm the absence of sex differences.

Baicailein administration was safe and well tolerated by healthy subjects from 100 mg to 2800 mg, with a low number of AEs being reported. The safety assessments used in our study based on preclinical safety data were, in general, recognized to be reliable and relevant for a Phase I study. The study included routine monitoring of subjects for clinical signs, hematology parameters, liver function tests (alanine transaminase, aspartate aminotransferase, and gamma-glutamyl transferase), kidney function tests (blood, urea, nitrogen; creatinine), ECG and urinalyses. No risks were identified according to evaluation of vital signs, ECG, or physical examination and there appeared to be no effect on the QIC interval. Adverse gastrointestinal events such as constipation and abdominal distention were expected due to disruption to intestinal microflora. Dry cough and hemolytic anemia, which occurred in preclinical toxicity tests, were not observed in clinical studies. All reported AEs were transient and mild in intensity. There was no evidence of a dose-related increase in AEs upon baicailein administration.

5. Conclusions

Multiple peaks on the plasma concentration–time curves for baicailein and baicalin were found at all doses tested. Dose proportionality was inconclusive in the dose range 100–2800 mg. Single oral doses of 100–2800 mg of baicailein were safe and well tolerated by healthy subjects. Clinical laboratory assessments showed no signs of toxicity in the liver or kidney. The favorable safety profile and PK properties warrant further clinical studies for baicailein.

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