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Pharmacokinetics, safety, and tolerability of single and multiple-doses of pinocembrin injection administered intravenously in healthy subjects

Guoying Cao [a], Pengyue Ying [c], Bei Yan [a], Wei Xue [a], Kexin Li [a], Aixin Shi [a], Taohua Sun [b], Jiling Yan [c], Xin Hu [a,*]

[a] Department of Clinical Pharmacology, Beijing Hospital, Beijing 100730, China
[b] School of Pharmaceutical Sciences, Shandong University, Jinan 250100, Shandong, China
[c] Zhongqi Pharmaceutical Technology (Shijiazhuang) Co. Ltd., Shijiazhuang 050051, China

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ABSTRACT

Ethnopharmacological relevance: Pinocembrin is the most abundant flavonoid in propolis. Preclinical studies have suggested that pinocembrin protects rat brain against oxidation and apoptosis induced by ischemia–reperfusion both in vivo and in vitro. To investigate the safety, tolerability and pharmacokinetics of a new neuroprotective agent, pinocembrin.

Materials and method: A double-blind, placebo-controlled, randomized study was carried out in 58 healthy subjects. Single ascending doses of pinocembrin (20–150 mg) were evaluated in 5 cohorts. Multi-dose was studied at pinocembrin 60 mg.

Results: Pinocembrin was well tolerated. No serious adverse events occurred. No subjects were discontinued because of a treatment emergent AE. Treatment related adverse event was acute urticaria. Two subjects in 150 mg cohort developed grade II urticaria during the study. One subject discontinued after 3 days at 60 mg bid because of diarrhea. In the single-dose study, the mean peak plasma pinocembrin concentration was obtained at the end of the 30-min infusion. The C_{max} ranged from 0.28 μg mL^{-1} to 2.46 μg mL^{-1}. AUC $_{(0,\infty)}$ ranged from 10.34 μg mL^{-1} min to 89.34 μg mL^{-1} min. The $T_{1/2}$ was similar across 5 dose groups, ranging from 40 to 55 min. Both urinary and feces excretion levels of pinocembrin were extremely low and similar among each dose groups, with mean values ranging from 0.07% to 0.17% and 0.94% to 1.94% of the administered dose, respectively. Linear increases in C_{max} and $AUC_{(0,\infty)}$ were observed. The pharmacokinetics of pinocembrin in multiple-dose was similar to those observed in the single-dose study, with no evidence of accumulation. Both urinary and feces excretion levels of pinocembrin were extremely low.

Conclusions: Pinocembrin displayed linear plasma pharmacokinetics over the dose range, 20–150 mg and was well tolerated up to 120 mg day^{-1} when administered intravenously to healthy adults. No major safety concerns were identified that would preclude further clinical development of pinocembrin injection.

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1. Introduction

Pinocembrin is the most abundant flavonoid in propolis. It was reported to have multiple actions including anti-platelet aggregant (Jantan et al., 2008), anti-angiogenic activities (Ahn et al., 2009), anti-inflammatory (Soromou et al., 2012), anti-oxidant (Kapoor, 2013; Santos et al., 1998; Yu et al., 2009), and antimicrobial (Paintz and Metzner, 1979). Recently, preclinical studies have suggested pinocembrin protects rat brain against oxidation and apoptosis induced by ischemia–reperfusion both in vivo and in vitro(Gao et al., 2008; Liu et al., 2008; Rasul et al., 2013; Shi et al., 2011; Soromou et al., 2012; Wang et al., 2013; Wu et al., 2013). Using a permanent focal cerebral ischemia rat model, pinocembrin improved regional cerebral blood flow and reduced the postischemic damage to the neurovascular unit at the dose level of 3, 10, and 30 mg kg^{-1}.

Pharmacokinetics, tissue distribution and vitro metabolism have been evaluated for pinocembrin in rat and dog (Yang et al., 2009). The major findings are summarized as follows, single injection doses (67.5, 22.5 and 7.5 mg kg^{-1}) of pinocembrin in rats, displayed a linear dose-exposure profile at three doses. The half-life of the parent drug

* Corresponding author.

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was 13.9, 14.6 and 7.3 min. Following a single injection of 22.5 mg kg^{-1} pinocembrin to rats, 0.1%, 2.1% and 26.3% of intravenous dose were recovered in bile, urine and feces respectively, indicated metabolism clearance was the primary route of excretion. After multiple injection doses (80 mg kg^{-1}) to dogs, there was a dose under-proportional increase in exposure and accumulation.

Based on our vitro metabolism study, pinocembrin showed a potent inhibition of CYP1A2 with IC50 values of 0.82 μM. Moderate inhibitions of CYP2C9 and CYP2C19 with IC50 values were 13.1 and 22.3 μM, respectively. Very little or no inhibition of CYP 2D6 and 3A4/5 was observed. No evidence of enzyme induction was detected in vitro. The metabolism of pinocembrin involves many enzymes, including CYP and UGT systems. However, overall UGT enzymes appear to play a major role in pinocembrin metabolism. The metabolism involves many enzymes, including CYP1A2, 2C9, CYP2E1 and CYP3A4 systems (not published).

This report describes the pharmacokinetic, safety, and tolerability results from a phase I, randomized, double blind, and placebo-controlled study conducted with healthy human subjects to explore escalating once-daily single and multiple-dose administration of pinocembrin injection.

2. Methods

2.1. Study population

This study was conducted according to the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice Guideline and the Guideline for Good Clinical Practice recommended by the State Food and Drug Administration (SFDA) of China.

The study protocol and the protocol amendments, as well as the informed consent form, the subject recruitment materials, and the investigator's brochure were reviewed and approved by the ethics committee of Beijing Hospital (Ethical approval record number is “2012L02508”).

Healthy subjects were recruited by the phase I clinical trial site at Beijing Hospital (Beijing, China) through the clinical site database. After signing informed consent forms, subjects underwent clinical examinations. Electrocardiogram and clinical chemistry were performed 2 to 7 days before admitting to the Clinical Research Center.

Criteria for eligibility included healthy male and female adults, aged 18–40 years, who were nonsmokers, and had a body mass index (BMI) between 19 and 25. All female subjects had negative pregnancy test results at screening. Male subjects had to use a two acceptable methods of contraception for the entire duration of the study, up to the study completion visit. Other exclusion criteria were as follows: any disease or condition that might interfere with the absorption, distribution, metabolism, or excretion of the study drug, a history of drug or alcohol abuse, blood donation (more than 400 mL) within the past 8 weeks, consumption of other prescribed or over the counterdrugs (vitamins or calcium supplements allowed) within 4 weeks before the study, participation in a similar study within the past 4 weeks, and a history of immunodeficiency disease, including a positive HIV test result, or a positive hepatitis B surface antigen or hepatitis C antibody. These criteria were confirmed by blood testing and patient reports. Routine clinical chemistry tests consisted of hemoglobin, hematocrit, total white blood cell count, blood glucose, triglycerides, total cholesterol, albumin, direct and indirect bilirubin, creatinine, AST, alkaline phosphates, lactic dehydrogenase, potassium, and urinalysis

2.2. Drugs

Pinocembrin, manufactured by Central Institute of Pharmaceutical Research Zhongqi Pharmaceutical Technology (Shijiazhuang) Co., Ltd. in 10 mg powder, with matching placebo.

2.3. Study design

This was a phase I, randomized, double-blind, placebo-controlled, parallel-group, single-dose escalation and multiple-dose clinical study to evaluate and compare the safety and PK of pinocembrin compared to placebo in healthy subjects. The single-dose study was designed to enroll 46 subjects into 5 cohorts at dose levels of 20, 40, 80, 120, or 150 mg. The multiple-dose study involved one group of subjects receiving either study drug or placebo from day 0 for 5 consecutive days.

In the single-dose study, doses of 20, 40, 80 mg were administered in 10 subjects, while doses of 120 and 150 mg were administered in 8 subjects. Subjects were randomly assigned to receive either pinocembrin injection ($n=8$ subjects in 20, 40, 80 mg and $n=6$ in 120, 150 mg) or placebo (0.9% normal saline in 100 ml; $n=2$ subjects in each group) administered intravenously (IV) over a 30-min infusion and were monitored for 48 h after the infusion. The principal investigator reviewed all safety data to determine if dose limiting toxicity had occurred. Once the safety of the prior cohort had been determined, the study drug was administered to subjects in the next dose level cohort. Each subject participated in up to a 7-day screening period, 48 h treatment periods, and a study completion evaluation.

In the multiple-dose study, 12 subjects were randomly assigned to receive either pinocembrin injection, 60 mg bid ($n=10$ subjects) or placebo (normal saline, $n=2$ subjects) on day 2, day 3, day 4 and a single morning dose on day 1 and day 5 for all cohorts.

Eligible subjects were admitted to the Clinical Research Center the day before dosing. No other food and drink other than that specified in the protocol was consumed at any time during the study. On the morning of dosing day, subjects were served a breakfast at 7:00. At 8:30 subjects were administered the study medication by a 30-min infusion. Series pharmacokinetics blood samples, urine and feces samples were completed during the 48 h period for the single-dose and up to 5 days for the multiple-doses.

2.4. Safety monitoring

Safety was assessed in both studies by vital signs, routine clinical chemistry, urinalysis, serum β2-microglobulin (β2-MG) and spontaneous reporting of adverse events (AEs) by the subjects. Heart rate and rhythm were monitored by dynamic electrocardioscanners prior to study drug administration, during infusion, and for 4 h postinfusion. AEs were recorded for the entire study duration. Investigators assessed all adverse events for severity, duration, outcome, and possible relationship to the study medication.

Renal function was assessed from BUN, serum creatinine measurements, and serum β2-MG. AEs were graded according to the DAIDS [http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf].

2.5. Pharmacokinetic evaluation

In the single-dose study, blood samples were obtained for measurement of pinocembrin plasma levels as follows: pre-dose, 10 min, 20 min, 30 min during infusion time and 10 min, 20 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h after infusion.

Urine samples were obtained at the following time intervals: pre-dose and 0–2, 2–4, 4–8, 8–12, 12–24 and 24–48 h after infusion.

In multiply dose study, blood samples were obtained from all subjects on day 1 and day 5, a full PK time course was obtained which included the following time points: pre-dose, 10 min, 20 min, 30 min during infusion time and 10 min, 20 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h and 8 h after the last administration intravenous infusion. Urine and feces from the different subjects

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