Pharmacokinetics, Safety and Tolerability of Triflusal and its Main Active Metabolite HTB in Healthy Chinese Subjects

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Abstract

Objective: Triflusal presents comparable antiplatelet activity to aspirin while presenting a more favourable safety profile, and is used in the treatment of thrombosis. The study aimed to evaluate the pharmacokinetics and safety of triflusal and its major metabolite 2-(hydroxyl)-4-(trifluoromethyl)- benzoic acid (HTB) in healthy Chinese subjects.

Methods: 30 healthy subjects were recruited in this randomized, single-center, and open-label, parallel, single ascending doses (300, 600, 900 mg) and multiple doses (600 mg, once daily for 7 days) study. Plasma samples were analyzed with a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method. Safety was assessed by adverse events, ECG, laboratory testing, and vital signs.

Results: Triflusal was safe and well tolerated. After single-dose administration, triflusal was rapidly absorbed with a mean T_{max} of 0.55–0.92 h and a mean $t_{1/2\ kel}$ of 0.35–0.65 h, HTB was absorbed with a mean T_{max} of 2.35–3.03 h and a mean $t_{1/2\ kel}$ of 52.5–65.57 h. C_{max} and AUC for triflusal and HTB were approximately dose proportional over the 300–900 mg dose range. In the steady state, the accumulation index (R) indicated that the exposure of triflusal increased slightly with repeated dosing, and the exposure of HTB increased obviously. 3 adverse events certainly related to the investigational drugs occurred in the multiple-dose phase.

Conclusion: Following oral dosing under fasting condition, triflusal is promptly absorbed and rapidly depleted from the systemic circulation. HTB is quickly generated from triflusal and slowly eliminated. Triflusal accumulates slightly in the body. HTB plasma concentration builds up progressively toward steady-state.

Introduction

Triflusal (2-acetoxy-4-trifluoromethyl benzoic acid; CAS 322-79-2) is a new molecule related to salicylic acid which is used in the prevention and treatment of thromboembolic disease [1,2]. Triflusal inhibits cycloxygenase-1 in platelets, but seems to leave intact the arachidonic acid metabolic pathway in endothelial cells. Trifusal and HTB stimulate the constitutive activity of NO synthase (cNOS) and consequently increase NO production by endothelial cells and leucocytes. Triflusal presents comparable antiplatelet activity to aspirin while presenting a more favourable safety profile [3].

Triflusal is absorbed in the small intestine and its bioavailability ranges from 83 to 100 % [1,4]. It binds to plasma proteins almost entirely (99 %) and crosses organic barriers readily. In humans, triflusal is deacetylated in the liver to HTB as the main active metabolite. And unchanged triflusal and HTB are eliminated primarily through the kidneys [5]. Unchanged triflusal, HTB and HTB glycine conjugate have been identified in the urine. Triflusal has 2 major pharmacological effects: in platelets it inhibits activation of thrombogenic mechanisms, while in the nervous system it blocks the main biochemical pathways that lead to cell damage during ischemia [3].

Following oral dosing, triflusal is promptly absorbed and rapidly depleted from the systemic circulation. Its concentration was measurable only up to 4 h after administration [2]. Main pharmacokinetic parameters of triflusal and HTB in healthy subjects of literature data [1,6,7] are summarized in **Table 1**. The pharmacokinetic profiles of triflusal or HTB do not appear to have clinically significant differences in elderly or

Table 1 Pharmacokinetics of triflusal and HTB in healthy subjects from literature data.

PK parameters[a]	300 mg [6] (n=9)	600 mg [7] (n=24)	900 mg [1] (n=8)
Triflusal			
C_{max} (μg/mL)	–	14.48 ± 7.22	11.61 ± 1.68
T_{max} (h)	–	0.875 (0.25–1.5)[b]	0.88 ± 0.26
$t_{l/2\ kel}$ (h)	0.64 ± 0.08	0.76 ± 0.64	0.53 ± 0.12
AUC_{0-t} (μg/mL·h)	3.0 ± 0.5	16.22 ± 7.58	–
HTB			
C_{max} (μg/mL)	–	65.51 ± 19.44	92.71 ± 17.14
T_{max} (h)	–	2 (0.75–12)[b]	4.96 ± 1.37
$t_{l/2\ kel}$ (h)	59.7 ± 11.3	43.13 ± 6.56	34.29 ± 5.32
AUC_{0-t} (μg/mL·h)	1321 ± 304	2877.97 ± 881.24	-

[a] Data were presented as mean ± SD
[b] Median (range)

younger volunteers [3,8]. No plasma accumulation of the parent compound was noticed in volunteers > 80 years old who received triflusal 300 mg × 2/day for 13 days [9]. Additionally, the steady-state level of HTB is reached within 8–10 days of treatment [10,11].

At present, no available data on pharmacokinetics of triflusal and HTB in Chinese subjects are reported. The objective of this study was to evaluate the pharmacokinetic profiles of triflusal and HTB after oral single doses (300, 600, 900 mg) and multiple doses (600 mg, once daily for 7 days) of triflusal capsules in healthy Chinese subjects. Moreover, the safety and tolerability of triflusal in Chinese subjects were also assessed.

Subjects and Methods

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Study approval

The clinical trial was licensed in State Food and Drug Administration in China with the registration number of 2010L01996. The study was performed at the Second Affiliated Hospital of Soochow University in Suzhou, China. The study was conducted in accordance with the principles of the Declaration of Helsinki [12] and Good Clinical Practice (GCP) in China [13], and the protocol was approved by the Independent Ethics Committee of the hospital with the approval number of 2013 (12). All study participants gave written informed consent before the conduct of the study-related procedures.

Materials and reagents

Triflusal reference standard (purity of 99.7%) and HTB reference standard (purity of 99.9%) were provided by Henan Furen pharmaceutical R & D Co., Ltd. (Henan, China). Triflusal capsules (300 mg; lot no. 201303012; expiration date, February 2015) were provided by Henan Furentang medicines Co., Ltd. (Henan, China). 6-methoxysalicylic acid (purity of 98.0%) used as an internal standard (IS) was purchased from Sigma (St. Louis, MO, USA).

Methanol, acetonitrile and formic acid were of HPLC grade, and purchased from Tedia Company, Inc. (Fairfield, OH, USA). Analytical-grade ammonium acetate was purchased from Nanjing Chemical Reagent Co. Ltd. (Nanjing, China). HPLC grade water was obtained from a Milli-Q water purification system (Millipore Co., Milford, MA, USA) and used throughout the study. The other chemicals and organic solvents were of analytical or HPLC grade and used without further purification.

Study population

Chinese healthy volunteers, aged 18–40 years, male and female (nonpregnant and nonlactating), weighing not less than 50 kg, body mass index (BMI) between 19 and 24 kg/m^2, were enrolled. Subjects were all in good health as determined by their past medical history, physical examination, vital signs, standard laboratory parameters (e.g. haematology, blood chemistry and urinalysis), and 12-lead ECG within 2 weeks before the first dosing of the study medication. Female subjects were required to have a negative pregnancy test at screening and to agree on using an effective contraception method during the study period.

The persons are excluded out of the study who are: infected of hepatitis B or C virus or HIV or Syphilis; pregnant or breastfeeding; having a history of or having pulmonary, cardiovascular, neurological, psychiatric, endocrine or coagulation disorders, having renal or hepatic disease or any physical attributes that may influence the trial results; medicated or using drugs of any kind in ≤ 2 weeks before the study commencement; having a history of or currently abusing of drugs or alcohol; smoking of more than 5 cigarettes per day or equivalent; participating in another drug study or donation of blood in ≤ 90 days prior to the study.

Study design

This was a randomized, single-center, open-label study in which 30 healthy subjects of either sex were randomly assigned to group 1, group 2, and group 3 (5 females and 5 males in each group). The subjects were hospitalized at 7:00 pm the night before dosing and required to fast overnight (10 h). Throughout the sequential single-dose and multiple-dose trials, triflusal was administrated in fasting state. After the trial, the subjects were released and visited the clinic for post-test of vital signs, 12-lead ECG, physical examination, and routine laboratory test. If the principal investigator determined that a subject required additional tests, the subject obeyed these orders.

Single dose administration

The therapeutic dose of triflusal capsule was 300 mg, 600 mg or 900 mg once daily. On day 1, subjects of group 1, group 2, and group 3 received a single oral administration of 300 mg, 600 mg, and 900 mg of triflusal capsules, respectively. Study medication was administered at 7:00 am with 250 mL of water. Water intake was prohibited within the following 2 h after drug administration and a standard lunch was served 4 h after dosing. Blood samples (4 mL each) were collected from vein vessels in the antebrachium predose (0 h) and 10, 20, 30 and 45 min, and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, 120 and 168 h after dosing. The blood samples were collected into sodium heparin-coated tubes, immediately kept in icebox, and centrifuged. Following centrifugation (4 000 rpm, 5 min, 4 °C), plasma samples were transferred to polyethylene tubes containing an aliquot of 20 μL of 3 M hydrochloric acid, immediately vortex-mixed for 10 s. After that, the plasma samples were centrifuged (16 000 rpm, 3 min, 4 °C), separated and transported into 2 EP tubes. The tubes were then labeled and stored at −70 °C until analysis.

Multiple dose administration

After single-dose phase from day 1–8, subjects of group 2 were assigned to receive 600 mg of triflusal capsules once daily from day 8 to day 14 in fasting state. On days 11, 12, 13, and 14, predose blood samples (4 mL each) were collected prior to the morning dose to evaluate the achievement of steady state condition. On day 14, blood samples were collected predose (0 h) and at the same time points as in the single-dose study to 168 h after dosing. All the other experimental conditions were in consistent with those in the single dose phase.

Plasma sample analysis

A simple, rapid and sensitive LC-MS/MS assay method was developed and validated for the simultaneous quantification of triflusal and HTB in human plasma. The method validation was carried out according to FDA guidance [14]. A 200 µL aliquot was mixed with 50 µL of the IS solution of 100.1 µg/mL. Then 800 µL acetonitrile was added. After vortex for 1 min, the sample was centrifuged at 16 000 rpm for 10 min at 4 °C. The supernatant of 100 µL was mixed with 1 mL of water in an auto-injector vial, and 20 µL aliquot was injected into the Agilent 1 200 Series HPLC system (Agilent Technologies, Palo Alto, CA, USA) for analysis. The chromatographic separation was achieved on an XTerra® RP 18 column (150 × 4.6 mm, 5 µm; Waters Corporation, MA, USA), with an isocratic solvent mixture [methanol-10 mM ammonium acetate (0.5 % formic acid contained), 64:36 (v/v)] at a flow rate of 1.0 mL/min. Quantification was achieved with MS-MS detection in negative ion mode for both the analytes and the IS using an MDS Sciex API-4000 mass spectrometer (Applied Biosystem Sciex, Ontario, Canada) equipped with a Turboionspray™ interface at 650 °C. The ion spray voltage was set at − 4 500 V. The source parameters, viz. the nebulizer gas, curtain gas, auxillary gas and collision gas, were set at 55, 35, 65 and 8 psi, respectively. The compound parameters, viz. the declustering potential, collision energy, entrance potential and collision exit potential, were − 9, − 8, − 10, and − 10 V for triflusal, − 60, − 52, − 10, and − 10 for HTB, and − 40, − 16, − 10, and − 16 V for IS. Detection of the ions was carried out in the multiple-reaction monitoring mode (MRM), by monitoring the transition pairs of m/z 246.9 precursor ion to the m/z 204.8 for triflusal, m/z 204.9 precursor ion to the m/z 160.8 product ion for HTB, and m/z 166.9 precursor ion to the m/z 123.0 product ion for IS. Quadrupoles Q1 and Q3 were set on unit resolution. The analysis data obtained were processed by Analyst software™ (version 1.4.2). The calibration curves obtained were linear ($r^2 \geq 0.99$) over the concentration range of 0.03–30 µg/mL for triflusal and 1–200 µg/mL for HTB, respectively. The intra- and inter-batch precisions for the quality control (QC) samples prepared at the low (0.06 µg/mL and 2 µg/mL for triflusal and HTB, respectively), medium (1.2 µg/mL and 16 µg/mL for triflusal and HTB, respectively) and high (24 µg/mL and 160 µg/mL for triflusal and HTB, respectively) concentrations ranged from 2.1 to 6.8 % and 1.8 to 7.5 %, respectively. Triflusal and HTB were stable at bench-top stability (3 h), repeated freeze – thaw cycles (3 cycles), and long-term stability at − 70 °C for 35 days.

Pharmacokinetic analysis

The pharmacokinetic parameters were estimated using non-compartmental pharmacokinetic methods with WinNonlin Professional software (Version 6.3, Pharsight Corporation, Mountain View, CA, USA). The pharmacokinetic parameters studied in the study included maximum plasma concentration (C_{max}), C_{max} at steady state (C_{ss-max}), time to reach C_{max} (T_{max}), minimum plasma concentration at steady state (C_{ss-min}), average value of the steady-state plasma concentration (C_{av}), elimination half-life ($t_{1/2\ kel}$), area under the plasma concentration-time curve (AUC) from time zero to t post-dosing (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), elimination rate constant (K_{el}), apparent clearance (CL/F), and the apparent total volume of distribution (Vd/F), accumulation index (R) and the degree of fluctuation (DF). C_{max}, T_{max}, C_{ss-max} and C_{ss-min} were obtained directly from the observed data. Kel was obtained as the slope of the linear regression of the terminal portion of the curve. $t_{1/2\ kel}$ was calculated as 0.693/Kel. $C_{av} = AUC_{ss}/\tau$ ($\tau = 24$). $R_{auc} = AUC_{ss}/AUC_{0-t}$ (AUC_{0-t} was the AUC calculated from zero to t post-dosing in the single dose phase). $R_{cmax} = C_{ss-max}/C_{max}$ (C_{max} was the maximum plasma concentration observed in the single dose phase). $DF = (C_{ss-max} - C_{ss-min})/C_{av}$.

Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0, SPSS, Inc, Chicago, Illinois). For the exploration of dose proportionality, the slope β and 90 % confidence intervals (CIs) obtained from the power model: ln (AUC or C_{max}) = $\alpha + \beta \times \ln$ (dose) were computed by covariance (ANCOVA) to quantify dose proportionality for triflusal and HTB. The pre-defined criterion (0.500, 2.000) is proposed for exploratory dose proportionality assessments across the complete dose range [15]. One-way ANOVA was also used to evaluate any differences in $t_{1/2\ kel}$, CL/F, and Vd/F among the single dose treatments. For T_{max}, non-parametric test (NPT) was used to evaluate the differences among dose groups. The paired t-test (PTT) was applied to evaluate whether the pharmacokinetic parameters were in concordance with those reported in the single-dose phase. Statistical significance was set at $P < 0.05$ in all the tests.

Summary statistics (number of subjects, means, standard deviations, minimum, maximum, etc.) of the demographic characteristics were calculated for each group.

Safety assessment

The safety of triflusal was evaluated by monitoring adverse events (AEs), laboratory parameters, vital signs and 12-lead ECG recordings. Vital signs were measured pre- and post-dose. After the trial, heart rate, blood pressure, 12-lead ECG, and body temperature were measured, and clinical examinations and routine laboratory tests were performed.

Results
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Study population

A total of 30 healthy Chinese subjects (15 males and 15 females) with age of 18–26 (mean ± SD, 23 ± 2 years), weight of 50.0–73.0 (57.0 ± 6.4 kg), height of 1.520–1.810 (1.650 ± 0.071 m) and body mass index (BMI) of 19.1–23.8 (20.9 ± 1.4 kg/m^2) were enrolled in the study after signing the informed consent form. Demographic parameters for subjects are summarized in **Table 2**. No subject halted the study or dropped out.

Pharmacokinetics

Single dose administration

The mean plasma pharmacokinetic variables for triflusal and HTB after single dose of 300, 600, 900 mg of triflusal capsules in fasting state are presented in **Table 3**, and the representative plasma concentration-time profiles are shown in **Fig. 1**.

Over the 300–900 mg dose range, C_{max} and AUC increased in proportion to the doses for both triflusal (r = 0.890, 0.934, and 0.876 for C_{max}, $AUC_{0-4\ h}$ and $AUC_{0-\infty}$, respectively) and HTB (r = 0.953, 0.952, and 0.764 for C_{max}, $AUC_{0-168\ h}$ and $AUC_{0-\infty}$, respectively). For triflusal, the mean slopes (90 % CIs) were 1.244 (1.040, 1.449) for C_{max}, 1.043 (0.915, 1.172) for AUC_{0-t}, and 0.935 (0.769, 1.101) for $AUC_{0-\infty}$. For HTB, The mean slopes (90% CIs) were 0.900 (0.807, 0.992) for C_{max}, 0.699 (0.561, 0.838) for AUC_{0-t}, and 0.650 (0.474, 0.826) for $AUC_{0-\infty}$. C_{max} and AUC for triflusal and HTB were approximately dose proportional over the 300–900 mg dose range. T_{max}, $t_{1/2\ kel}$, Vd/F and CL/F were independent of dose for triflusal ($P > 0.05$), which indicated kinetic linearity for triflusal. For HTB, significant differences ($P < 0.05$) were found in $t_{1/2\ kel}$ between dose of 300 and 600 mg, Vd/F between dose of 300 and 900 mg, CL/F between dose of 300 and 600 mg, and CL/F between group dose of 300 and 900 mg. No significant differences were found in T_{max} for HTB.

Multiple dose administration

The representative plasma concentration-time profiles after receiving 600 mg triflusal capsules once daily for 7 consecutive days in fasting state are shown in ▶ **Fig. 2**. The pharmacokinetic parameters of triflusal and HTB after oral multiple-dose administration were summarized in ▶ **Table 3**.

Triflusal disappeared rapidly from the systemic circulation, and most drug concentrations dropped below the limit of detection of the analytical method 4 h after administration. Trough plasma concentrations of triflusal were zero. No significant differences ($P > 0.05$) in trough plasma concentrations of HTB before the morning dose among repeated administration days 4, 5, 6, and 7 were found, suggesting that steady-state condition was achieved after multiple doses of 600 mg triflusal capsules once daily for 3 days. The R_{auc} (triflusal 1.5 ± 0.3, HTB 2.1 ± 0.2) and R_{cmax} (triflusal 1.5 ± 0.5, HTB 1.9 ± 0.3) showed the exposure of triflusal increased slightly with repeated dosing, and the exposure of HTB increased obviously with repeated dosing.

For triflusal, no significant differences ($P > 0.05$) in pharmacokinetic parameters ($t_{1/2\ kel}$, T_{max}, Vd/F) and significant differences ($P < 0.05$) in pharmacokinetic parameters (C_{max}, AUC, CL/F) were observed between single- and multiple-dose phase. For HTB, no significant differences ($P > 0.05$) in pharmacokinetic parameters ($t_{1/2\ kel}$, T_{max}) and significant differences ($P < 0.05$) in pharmacokinetic parameters (C_{max}, AUC, CL/F, Vd/F) were observed between single- and multiple-dose phase.

Safety

Safety data were available for all 30 subjects. Good tolerability was observed in all the treatment periods. All adverse events (n = 3) occurred in the multiple-dose phase. All the 3 subjects presented mild gastrointestinal discomfort after several doses administration, and the AEs were certainly related to the investigational drugs. Both effects disappeared spontaneously after several hours. No clinically significant changes in physical

Table 2 Demographic data of the 30 Chinese subjects.

Characteristics	Group 1 (300 mg)	Group 2 (600 mg)	Group 3 (900 mg)
n	10	10	10
Gender			
Male	5	5	5
Female	5	5	5
Age (y)	23 ± 2	23 ± 3	23 ± 2
Weight (kg)	57.6 ± 7.2	58.5 ± 6.4	59.2 ± 6.1
Height (m)	1.656 ± 0.058	1.659 ± 0.091	1.666 ± 0.070
BMI (kg/m²)	21.0 ± 1.7	21.2 ± 1.2	21.3 ± 1.4

BMI = Body mass Index
Data were presented as mean ± SD

Table 3 Pharmacokinetics of triflusal and HTB after oral single-dose and multiple-dose administration.

PK parameters	Single-dose			Multiple-dose
	300 mg (n = 10)	600 mg (n = 10)	900 mg (n = 10)	600 mg (n = 10)
Triflusal				
C_{max} (μg/mL)	5.005 ± 1.736	11.97 ± 3.92	18.79 ± 3.70	16.86 ± 4.92
T_{max} (h)	0.85 ± 0.76	0.92 ± 1.13	0.55 ± 0.34	0.53 ± 0.35
$t_{l/2\ kel}$ (h)	0.59 ± 0.50	0.65 ± 0.64	0.35 ± 0.07	0.44 ± 0.07
Kel (1/h)	1.855 ± 0.993	1.752 ± 0.899	2.081 ± 0.406	1.629 ± 0.242
CL/F (L/h)	40.87 ± 11.05	43.04 ± 9.42	42.84 ± 8.69	28.44 ± 4.51
Vd/F (L)	29.37 ± 16.18	38.23 ± 34.63	21.12 ± 4.92	17.67 ± 2.81
$AUC_{0-4\ h}$ (μg/mL·h)	6.855 ± 1.308	13.63 ± 2.40	21.72 ± 4.36	20.63 ± 2.69
$AUC_{0-\infty}$ (μg/mL·h)	7.987 ± 2.848	14.55 ± 3.20	21.79 ± 4.37	21.55 ± 3.19
$AUC_{0-4\ h}/AUC_{0-\infty}$ (%)	90.2 ± 17.3	95.1 ± 11.1	99.7 ± 0.2	96.5 ± 9.9
$AUMC_{0-4\ h}$	9.516 ± 3.441	14.81 ± 4.48	22.58 ± 8.40	23.27 ± 5.35
$AUMC_{0-\infty}$	16.391 ± 16.096	20.55 ± 18.15	22.86 ± 8.52	27.72 ± 17.47
MRT_{0-4h} (h)	1.38 ± 0.42	1.10 ± 0.33	1.02 ± 0.24	1.15 ± 0.32
$MRT_{0-\infty}$ (h)	1.78 ± 1.05	1.32 ± 0.79	1.03 ± 0.25	1.25 ± 0.59
HTB				
C_{max} (μg/mL)	46.59 ± 6.42	85.35 ± 13.35	125.4 ± 15.6	163.1 ± 13.4
T_{max} (h)	3.03 ± 1.25	2.65 ± 0.63	2.35 ± 0.88	2.50 ± 1.37
$t_{l/2\ kel}$ (h)	65.57 ± 15.12	52.50 ± 9.61	58.21 ± 15.96	53.35 ± 7.1
Kel (1/h)	0.011 ± 0.002	0.014 ± 0.003	0.013 ± 0.003	0.013 ± 0.002
CL/F (L/h)	0.087 ± 0.023	0.120 ± 0.029	0.125 ± 0.028	0.057 ± 0.013
Vd/F (L)	7.847 ± 1.068	8.836 ± 1.390	10.02 ± 1.42	4.341 ± 0.665
$AUC_{0-168\ h}$ (μg/mL·h)	3025 ± 644	4646 ± 944	6575 ± 1388	9663 ± 1786
$AUC_{0-\infty}$ (μg/mL·h)	3694 ± 1063	5252 ± 1250	7642 ± 2224	10865 ± 2212
$AUC_{0-168\ h}/AUC_{0-\infty}$ (%)	83.4 ± 6.5	89.2 ± 4.3	87.4 ± 6.3	89.3 ± 2.9
$AUMC_{0-168\ h}$	176383 ± 49567	248160 ± 66329	350783 ± 102578	507336 ± 121313
$AUMC_{0-\infty}$	360666 ± 190915	400021 ± 158591	638067 ± 383560	805539 ± 239205
$MRT_{0-168\ h}$ (h)	57.60 ± 4.69	52.80 ± 4.29	52.75 ± 4.33	52.02 ± 3.33
$MRT_{0-\infty}$ (h)	92.64 ± 21.64	73.85 ± 13.40	78.83 ± 20.52	72.84 ± 9.18

Data were presented as mean ± SD

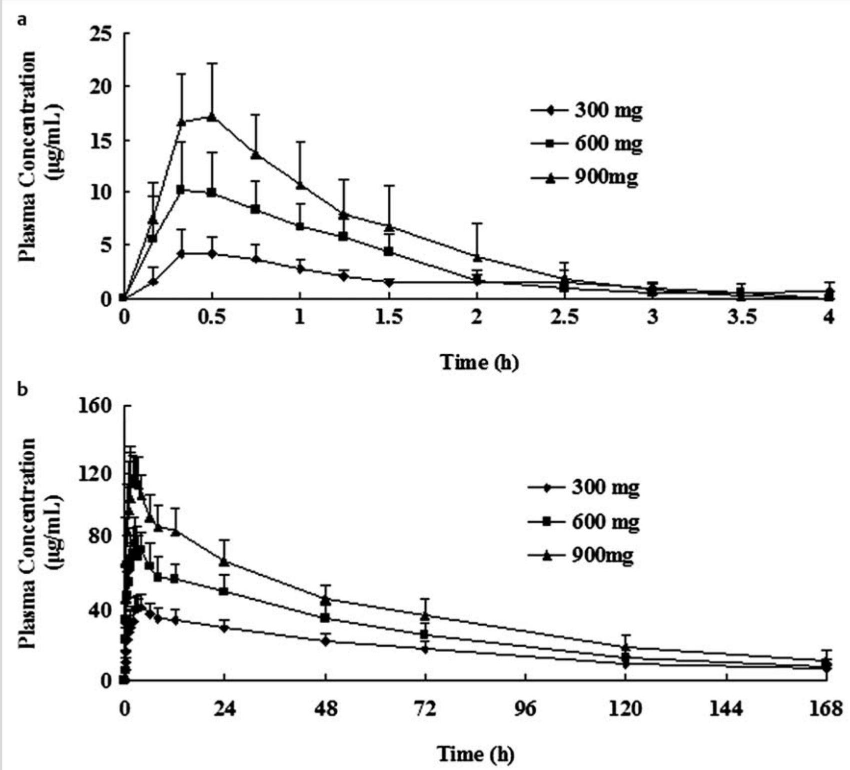

Fig. 1 Plasma concentration-time curves of triflusal **a** and HTB **b** following single doses of triflusal capsules. Data were presented as mean ± SD.

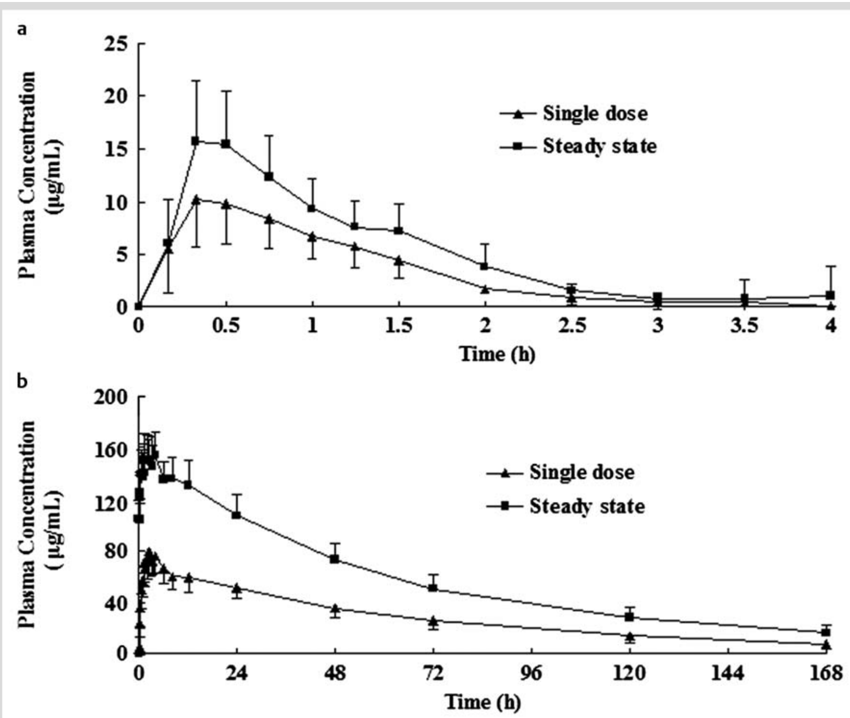

Fig. 2 Plasma concentration-time curves of triflusal **a** and HTB **b** following a single dose or multiple doses (steady state) of 600 mg triflusal capsules for 7 days. Data were presented as mean ± SD.

examination, vital signs, 12-lead ECG and safety laboratory testing were observed.

Discussion

The study evaluated the pharmacokinetic and safety profiles of triflusal and its main metabolite HTB following single doses (300, 600, 900 mg) and multiple doses (600 mg, once daily for 7 days) in 30 healthy Chinese subjects.

The results showed that triflusal disappeared rapidly from the systemic circulation, whereas HTB was slowly eliminated. Plasma concentration of triflusal was no longer detectable at 4 h after oral administration, which was consistent with previous reports about triflusal [2,16]. Triflusal did not accumulate in the body, while HTB plasma concentration built up progressively towards steady state levels, apparently achieved after 3 days of treatment with the dose regimen proposed.

In the single-dose phase, no adverse event occurred. Over the 300–900 mg dose range, C_{max} and AUC of triflusal and HTB increased linearly by linear regression analysis. T_{max} of triflusal and HTB were dose-independent. The mean $t_{1/2\ kel}$ of triflusal and HTB were similar across all doses. The main pharmacokinetic parameters of triflusal and HTB following single doses (300 mg and 600 mg) of triflusal capsules are consistent with previous reports [6,7]. In the single dose of 900 mg study, the $t_{1/2\ kel}$ of trifusal and HTB were 0.35 ± 0.07 h and 58.21 ± 15.96 h, the C_{max} of trifusal and HTB were 18.79 ± 3.70 µg/mL and 125.4 ± 15.6 µg/mL, and T_{max} of trifusal and HTB were 0.55 ± 0.34 h and 2.35 ± 0.88 h. However, Ramis et al. [1] reported the $t_{1/2\ kel}$ of trifusal and HTB were 0.53 ± 0.12 h and 34.29 ± 5.32 h, the C_{max} of trifusal and HTB were 11.6 ± 1.68 µg/mL and 92.71 ± 17.14 µg/mL, and the T_{max} of trifusal and HTB were 0.88 ± 0.26 h and 4.96 ± 1.37 h.

In the multiple-dose phase, 3 subjects presented mild gastrointestinal discomfort after several doses administration, and the adverse events were certainly related to the investigational drugs. Trough plasma concentrations of triflusal were zero. No significant difference in C_{ss-min} of HTB was found by ANOVA analysis. The T_{max} and $t_{1/2\ kel}$ of trifusal and HTB showed no significant differences between the first and the last dose. The C_{max} and AUC of trifusal were slightly higher in multiple-dosing administration than the corresponding values obtained after single-dose administration, and slight accumulation was found following repeated dosing (R_{cmax} 1.5 ± 0.5 and R_{auc} 1.5 ± 0.3). However, HTB increased obviously with repeated dosing (R_{cmax} 1.9 ± 0.3 and R_{auc} 2.1 ± 0.2). No available data on pharmacokinetics of triflusal following multiple doses are reported. The main pharmacokinetics parameters of HTB following multiple doses (600 mg, once daily for 7 days) of triflusal capsules are consistent with previous reports [17]. However, the T_{max} of HTB achieved in previous study [17] were more delayed (median (range), 4 (1–10) h), compared with the findings in our study (median (range), 2 (0.75~4) h) and other previous reports [10,16].

Conclusions

Triflusal capsule was safe and well tolerated in this study. No clinically significant changes in physical examination, vital signs, 12-lead ECG and safety laboratory testing were observed. The most frequently occurring adverse event certainly related to the investigational drugs was gastrointestinal discomfort after multiple doses. The plasma concentration of HTB reached its steady-state condition after multiple doses of 600 mg triflusal capsules once daily for 3 days. The exposure of triflusal increased slightly, and the exposure of HTB increased obviously with repeated dosing.

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Conflict of Interest

The authors state no conflict of interests in relation to the present study.

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