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ORIGINAL RESEARCH

Pharmacokinetics and Safety of Fospropofol Disodium for Injection in Subjects with Hepatic Impairment Compared with Healthy Matched Controls: A Prospective Cohort Study

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Purpose: Fospropofol disodium for injection ($Fospropofol_{FP}$) is a new water-soluble propofol prodrug for procedural sedation and general anesthesia. This prospective cohort study aimed to characterize the pharmacokinetics and safety of $Fospropofol_{FP}$ in subjects with hepatic impairment compared with healthy matched participants during general anesthesia.

Patients and Methods: Twenty-three patients were enrolled and divided into three cohorts according to liver function: normal liver function (n = 10), moderate hepatic impairment (n = 10), and severe hepatic impairment (n = 3). They received a single bolus of $Fospropofol_{FP}$ 10 mg/kg i.v. Venous blood samples were collected from each patient 14 time points. The plasma concentrations of $Fospropofol_{FP}$ and active metabolite propofol were determined by liquid chromatography tandem mass spectrometry (LC-MS/MS). The pharmacokinetic parameters were calculated by non-compantmental analysis (NCA) using Phoenix WinNonlin software.

Results: Compared with matched healthy controls, patients with moderate hepatic impairment exhibited significant reduced exposure and increased elimination for $Fospropofol_{FP}$: the area under the curve (AUC) decreased by approximately 43% and clearance (CL) increased by 60%. The AUC of patients with severe hepatic impairment exhibited a significant decrease by approximately 55%. Notably, propofol (active metabolite) clearance decreased by approximately 15% and 33% in moderate and severe impairment, respectively. Multivariate analysis identified preoperative albumin (ALB) as an independent predictor of $Fospropofol_{FP}$ exposure.

Conclusion: Our study is the first to report altered PK of $Fospropofol_{FP}$ in patients with moderate-to-severe hepatic impairment, report a reverse pattern of increased elimination of $Fospropofol_{FP}$ and slow elimination of the metabolite propofol, and identify ALB as an independent predictor of $Fospropofol_{FP}$'s PK. No unexpected adverse events related to $Fospropofol_{FP}$ were seen in subjects with hepatic impairment after a single dose and that repeated dosing may need further evaluation.

Keywords: hepatic impairment, fospropofol disodium, pharmacokinetic, propofol, safety

Introduction

The liver serves as the principal organ for drug elimination, orchestrating critical metabolic pathways, including oxidation, reduction, and conjugation, that govern the pharmacokinetics (PK) of intravenous anesthetics.[1,2] Hepatic impairment disrupts the drug absorption, distribution, metabolism, and excretion by reducing hepatic blood flow, metabolic enzyme activity, and drug binding to plasma protein.[3] For instance, while ciprofol and remimazolam require no dose adjustment in mild-to-moderate hepatic impairment (Child-Pugh A/B), their use in severe dysfunction (Child-Pugh C) remains cautiously limited.[4,5] Similarly, propofol target-controlled infusion (TCI) at 3 μg/mL may provoke hemodynamic instability in advanced liver disease.[6] Notably, anesthesia induction itself reduces hepatic blood flow by

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35–42% in healthy individuals.[7] Therefore, it is crucial to develop individualized intravenous anesthetic strategies guided by PK characteristics for this vulnerable population.

Fospropofol$_{FP}$ (Yichang Humanwell Pharmaceutical Co., Ltd., Hubei, P. R. China), a water-soluble prodrug of propofol, addresses key limitations of conventional lipid-based propofol formulations. Upon administration, Fospropofol$_{FP}$ is rapidly hydrolyzed by endothelial alkaline phosphatase (ALP) to release propofol, which exerts sedative effects via GABA receptor potentiation and NMDA receptor inhibition. Compared to propofol, Fospropofol$_{FP}$ offers prolonged duration of action, enhanced hemodynamic stability, and elimination of lipid emulsion-related adverse reactions.[8] Substantial clinical evidence supports Fospropofol$_{FP}$ as an efficacious and well-tolerated agent for procedural sedation and general anesthesia.[9–13]

Current guidelines for Fospropofol$_{FP}$ lack evidence-based recommendations for hepatic impairment populations.[14,15] Specifically, no prior studies have systematically evaluated its PK in moderate-to-severe (Child-Pugh B/C) liver dysfunction or assessed the resulting exposure to its active metabolite, propofol. Additionally, hepatic impairment elevates ALP activity due to cholestasis and reduces albumin-binding capacity, which results from decreased synthesis, structural changes, and competition from endogenous substances. Furthermore, drug administration techniques, including needle insertion force, injection rate, and needle characteristics, can significantly influence drug dispersion and deposition patterns. Recent ex vivo and cadaveric studies have shown that the forces associated with bolus injection and continuous infusion techniques, as well as the choice of needle and injection rate, play a critical role in determining the spread of injectate.[16,17] Our findings aim to explore the PK characteristics of Fospropofol$_{FP}$ in patients with hepatic impairment, ensuring safer anesthesia management in this high-risk population. We hypothesized that moderate-to-severe liver dysfunction, which can alter enzyme function, would significantly accelerate the hydrolysis of Fospropofol$_{FP}$, leading to reduced drug exposure and accelerated elimination.

Materials and Methods

Design

This study was approved by the Committee on Ethics, at West China Hospital of Sichuan University (No.2024551), and was conducted there itself. Written consent was obtained from all patients. Registration number is CTR2400085355 in China. The study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki.

This study employed a single-center, non-randomized, open-label, single-adaptive "Reduced Design" clinical trial planned to be carried out in three phases. The protocol stipulated initial pharmacokinetic comparison between moderate hepatic impairment subjects and matched healthy controls, with subsequent exclusion of mild hepatic impairment assessment contingent upon demonstrating no clinically significant pharmacokinetic disparities. Hepatic function stratification utilized the Child-Pugh scoring system. Phase I enrolled ten subjects with moderate hepatic dysfunction (Child-Pugh 7–9) alongside ten demographically matched healthy controls. Interim pharmacokinetic analysis revealed <2-fold difference in systemic exposure parameters (AUC or C_{max}) of Fospropofol$_{FP}$ between cohorts, thereby obviating the need for Phase II implementation. The final phase (Phase III) evaluated three subjects with severe hepatic impairment (Child-Pugh 10–15) using dosing regimens guided by PK and safety profiles derived from the moderate hepatic impairment cohort in Phase I.

The sample size was determined using the PK guidance for patients with hepatic impairment and data from similar PK studies.

Participants

Our study included 24 participants scheduled to undergo endoscopy between July 2024 and December 2024. Patients were screened within 14 days before dosing in the hepatic impairment trial. Inclusion criteria: ① Patients undergoing painless endoscopy or treatment under quasi-general anesthesia; ② Age 18–65 years old, gender unlimited, BMI 18–30 kg/m^2; ③ Subjects with liver dysfunction: Child-Pugh was used to classify patients with liver damage. Subjects with normal liver function: gender, age, and BMI matched those with liver dysfunction (age ± 5 years, BMI ± 15%); ④ Can understand the process and method of this study, voluntarily participate in and sign the informed consent. Exclusion

Table 1 Child-Pugh Improved Grading Standard

Index	The Degree of Anomaly is Scored		
	1 Points	2 Points	3 Points
Hepatic encephalopathy	Not have	Phase 1–2	Phase 3–4
Ascites	Not have	Mild	Moderate and above
Serum bilirubin (umol/L)	<34.2	34.2–51.3	>51.3
Serum albumin (g/L)	≥35	28–34	<28
Prothrombin time(second)	<=14	15–17	≥18

Note: Grading standard: Grade A:5–6 points; Grade B:7–9 points; Grade C:10–15 points.

criteria: ① In addition to liver disease, other serious organic diseases, such as severe renal insufficiency; ② Predicted difficulty in ventilation or intubation (modified Mallampati score level III or IV); ③ Patients who drank alcohol within 48 hours before participating in the study; ④ Have a history of drug abuse, alcoholism or drug dependence (such as abuse or long-term use of sedative, analgesic drugs, etc); ⑤ People with a history of mental illness; ⑥ Patients who have participated in any drug clinical trial within 1 month before screening; ⑦ Pregnant and lactating women, fertile women or men are not willing during the entire trial period Contraception, for subjects (including male subjects) who plan to become pregnant within 1 month after the trial; ⑧ Participants who have any other factors deemed inappropriate by the investigator to participate in this study.

According to the preoperative liver function level, the patients were divided into 3 groups with normal liver function, moderate and severe hepatic impairment (Table 1).

Conduct of Anesthesia

All subjects fasted for at least 8 hours and abstained from drinking for 2 hours before examination. On the day of examination, two intravenous channels were established after the subjects entered the preparation room for drug administration and venous blood samples were collected, respectively. Electrocardiograph (ECG), blood pressure, pulse oxygen saturation, bispectral index monitoring were completed, continuous nasal catheter oxygen inhalation was performed for 5 L/min, and PK blood samples were collected before a single administration. The starting point of Fospropofol$_{FP}$ was recorded as 0min. Fospropofol$_{FP}$ (10 mg/kg) was administered intravenously over 60 seconds, preceded by sufentanil (0.1 μg/kg) to mitigate procedural discomfort (60s).

Blood Sample Collection

Venous blood samples (4mL) were drawn from the contralateral arm vein and placed in a tube containing K_2-ethylene-diamine-tetra-acetic acid as an anticoagulant before intravenous administration and 1, 2, 3, 5, 7, 9, 11, 15, 30, 60, 120, 240, and 480 minutes after intravenous administration of Fospropofol$_{FP}$. The sampling timepoints were designed to capture the complete PK profile of both Fospropofol$_{FP}$ and its active metabolite, propofol, based on prior literature and standard PK guidelines.[14,18] The obtained samples were centrifuged (2,000 × g, 4°C, 10 min), and the separated plasma samples were stored in sample tubes and spare tubes (no less than 12μL respectively) at −80°C for analysis.

Determination of Drug Concentration

The concentrations of Fospropofol$_{FP}$ and propofol (active metabolite) in human plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The LC-MS/MS system consists of a Shima Fluid Chromatograph and a QTRAP 5500 mass spectrometer.

Pharmacokinetic Analysis

The PK parameters were analyzed based on a noncompartmental analysis (NCA) using WinNonlin software 8.3. The analyte concentrations below the limit of quantification were set to zero. Fospropofol$_{FP}$ and propofol concentrations were obtained from the participants, plasma drug concentration–time data were fitted to determine $AUC_{(0\rightarrow t)}$ and $AUC_{(0\rightarrow\infty)}$,

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$T_{1/2}$, CL, $MRT_{(0\rightarrow t)}$ and $MRT_{(0\rightarrow\infty)}$ and the apparent volume of distribution (V_d). The values for C_{max} of $Fospropofol_{FP}$ and the time to reach C_{max} (T_{max}) were obtained from the observed data using the concentration–time curve.

Pharmacodynamics (PD) and Safety Assessments

The number of subjects with loss of consciousness (LOC, defined as Modified Observer's Assessment of Alertness/Sedation Scale [MOAA/S] <2), the duration of LOC, and the time to recovery of consciousness (time from the end of administration to the last point when the trial subject was fully awake) were summarized.

Adverse events, physical examinations, vital signs, laboratory tests, and 12-lead electrocardiograms were conducted. The clinical characteristics, severity, onset time, endtime, duration, management measures, and outcomes of adverse events were recorded, and their correlation with the study drug was determined. Adverse event severity was assessed according to the Common Terminology Criteria for Adverse Events version 5.0. Treatment-emergent adverse events (TEAEs) were continually monitored during the 2-day and a follow-up phone call on day 7 after the initial dose of $Fospropofol_{FP}$.

Statistics

GraphPad Prism 8.0.1 was used for drawing plasma concentration–time curves. Statistical analysis was all conducted using STATA18.0, and findings were considered statistically significant if P-value was less than 0.05. All quantitative data were tested for normality by Shapiro–Wilk test of STATA software. According to their distribution, the quantitative data were expressed as mean ± standard deviation (SD) or median (Q25, Q75). The normally distributed data were assessed by one-way ANOVA analysis of variance followed by Dunnett *t*-test or least significant difference *t*-test while other quantitative data were analyzed by the Kruskal–Wallis test. Considering the small sample size (n = 3) of the severe liver injury group (Child-Pugh C), all intergroup comparisons involving this group were performed using non-parametric tests. Univariate associations between basic information of patients and main PK parameters of $Fospropofol_{FP}$ were performed to obtain Pearson's correlation coefficients (r). Subsequently, clinical factors with *P* values <0.05 in the univariate analysis were examined in a multivariate analysis using multiple linear regression analysis.

Results

Demographics and Characteristics of Patients

Total of 24 patients were collected and 23 were included in the study, one excluded due to missing data. Finally, 23 patients were included. There were 19 men and 4 women, aged between 27 and 64, weighing 49–89 kg. The patients were divided into three groups, 10 patients had normal liver function, and the rest had some degree of liver dysfunction (10 patients had moderate and 3 patients had severe liver dysfunction, respectively). The levels of Weight, GGT, ALB, PT, INR in moderate/severe hepatic insufficiency group were significantly higher or lower than those in normal hepatic function group ($P < 0.05$). Patient demographics and clinical characteristics were summarized in Table 2.

Pharmacokinetics $Fospropofol_{FP}$

After a single intravenous injection of 10 mg/kg $Fospropofol_{FP}$, the average plasma concentration–time curve and semi-logarithmic curve of $Fospropofol_{FP}$ in subjects with normal liver function, moderate liver dysfunction, and several liver dysfunctions are shown in Figure 1. The main PK parameters are detailed in Table 3. Compared with the normal liver function group, the concentration of the moderate-to-severe hepatic insufficiency group decreased rapidly, and the changes of T_{max} and V_d in the three groups were similar, and $AUC_{(0\rightarrow 8h)}$, $AUC_{(0\rightarrow\infty)}$, were significant differences. $T_{1/2}$, C_{max}, $MRT_{(0\rightarrow 8h)}$, $MRT_{(0\rightarrow\infty)}$, were significantly decreased in the moderate liver dysfunction group compared to the normal liver function group.

Propofol

After a single intravenous injection of 10 mg/kg $Fospropofol_{FP}$, the average plasma concentration–time curve and semi-logarithmic curve of propofol in subjects with normal liver function, moderate liver dysfunction, and severe liver

Table 2 Demographics and Laboratory Biochemical Index

Characteristic	Normal Liver Function (n=10)	Moderate Liver Dysfunction /Grade B (n=10)	Severe Liver Dysfunction /Grade C (n=3)
Gender (Male/Female)	8/2	8/2	3/0
Age(years)	54.50(16.75)	56.00(13.00)	41.00(30.00)
Body height(m)	1.67±0.08	1.66±0.06	1.67±0.11
Weight(kg)	71.00±13.42	61.60±7.68*	57.00±7.81
ALT(U/L)	31.20(25.45)	30.50(59.50)	71.00(352.00)*
AST(U/L)	23.60(11.53)	40.50(52.00)	109.00(107.00)**
GGT(U/L)	25.85(20.00)	122.50(184.75)**	76.00(85.00)*
ALP(U/L)	94.20(40.86)	111.00(90.75)	149.00(71.00)
ALB(g/L)	44.65(2.70)	34.70(9.35)**	30.90(9.70)*
TBIL(μmol/L)	11.54(6.50)	32.70(30.63)**	113.40(137.20)*
SCr(μmol/L)	73.24±15.67	78.00±12.68	79.33±13.65
BUN(mmol/L)	5.97±0.93	5.25±2.13	4.60±2.52
PT(s)	11.57±0.78	14.12±1.62***	17.37±1.68***
INR	1.01(0.08)	1.21(0.30)***	1.47(0.41)*

Notes: *$P<0.05$, **$P<0.01$,*** $P<0.001$, compared to control group with normal liver function. Values are expressed as mean ±SD or median (IQR).
Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; ALB: Albumin; TBIL: total bilirubin; SCr: serum creatinine; BUN: blood urea nitrogen; PT: Prothrombin time.

dysfunction are shown in Figure 2. The main PK parameters are detailed in Table 4. The CL progressively declined, and other indicators were similar among the different groups.

PD and Safety

Loss of consciousness occurred in 5/10 (50%) of healthy control subjects, 10/10 (100%) of subjects in the moderately hepatically impaired group, and 3/3 (100%) subjects in the severely hepatically impaired treatment group after administration of $Fospropofol_{FP}$ 10 mg/ kg i.v. The duration of LOC was longer in healthy subjects (4min) compared with the hepatically impaired group (moderate 2.8 min, severe 2.7min), the recovery to a fully awake state of consciousness was

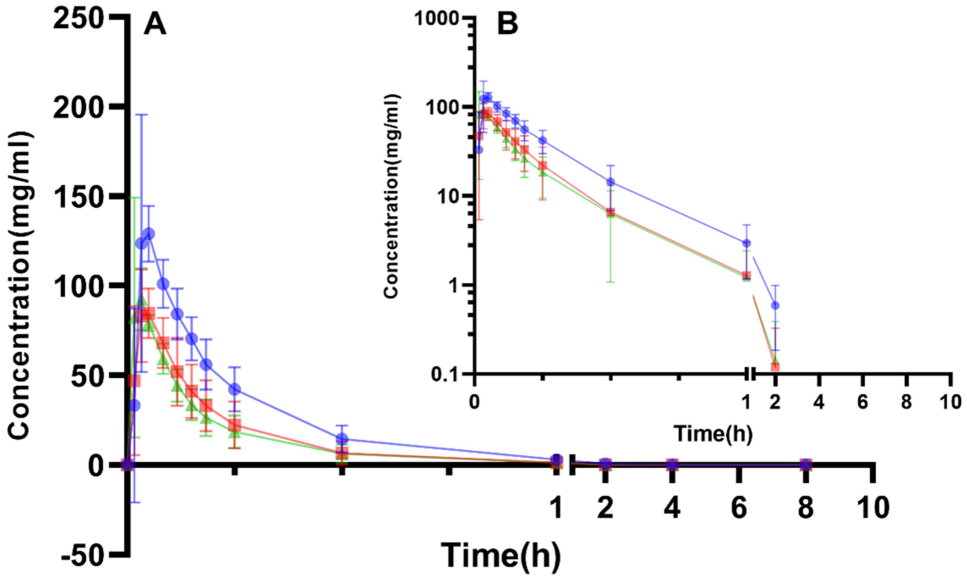

Figure 1 $Fospropofol_{FP}$ Plasma concentration-time profile(**A**) linear scale and (**B**) semi-log scale. Line blue: Normal Liver Function (n=10); Line Red: Moderate Liver Dysfunction (n=10); Line Green: Severe Liver Dysfunction (n=3).

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Table 3 PK Parameters in Patients with Various Degrees of Hepatic Impairment (Fospropofol$_{FP}$)

Index	Unit	Normal Liver Function (n=10)	Moderate Liver Dysfunction /Grade B (n=10)	Severe Liver Dysfunction /Grade C (n=3)
$AUC_{(0\rightarrow 8h)}$	h*ng/mL	31755.88±8794.45	18,132.43±8400.89**	14,396.67(8163.75)*
$AUC_{(0\rightarrow\infty)}$	h*ng/mL	31932.49±8904.74	18,254.73±8437.99**	14,521.60(8205.17)*
$T_{1/2}$	h	0.27±0.05	0.18±0.08**	0.17(0.12)
Tmax	h	0.04(0.02)	0.05(0.02)	0.03(0.03)
Cmax	ng/mL	132.00(46.50)	97.25(27.40) ***	101.00(58.10)
MRT(0→8h)	h	0.27±0.04	0.20±0.07**	0.15(0.17)
MRT (0→∞)	h	0.28±0.05	0.21±0.07**	0.16(0.17)
Cl_obs	L/h	24.03±8.34	38.37±13.03**	36.77(21.72)
Vd	L	9.52±3.85	8.85±1.86	9.41(2.67)

Notes: *P <0.05, **$P<0.01$, *** $P<0.001$, compared to control group with normal liver function. Values are expressed as mean ±SD or median (Q25,Q75).

Abbreviations: AUC, area under the concentration–time curve; $T_{1/2}$, elimination half-life; T_{max}, time of peak concentration; C_{max}, maximum concentration; MRT, mean residence time; CL_obs, Observed total clearance; $V_{d,}$ Volume of Distribution.

similar for healthy control subjects (22.91 min) and in the moderate hepatically impaired group (21.09 min), but it was prolonged in the severe hepatic impaired groups (25.51min).

The safety profile of Fospropofol$_{FP}$ was comparable among all groups. Subjects in the hepatic impairment treatment groups reported a slightly higher incidence of TEAEs (4/10 subjects [40%] with one TEAEs in the moderate hepatic impairment group and 1/3 subjects [33%] with one TEAEs in the severe hepatic impairment group) compared with healthy control subjects (3/10 subjects [30%] with two TEAEs). The most commonly reported events considered related to study drug were paresthesias such as pruritus, sensation of heat, electrical sensation, prickling, and biting, which were experienced in the perineal region, lower body, or torso and were mainly mild in severity and occurred in normal hepatic function group. However, only hypotension (defined as systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg for >1 minute) was found in hepatic impairment groups. There were no deaths, serious AEs, or discontinuations due to AEs reported in all groups. No relevant changes were noticed regarding clinical laboratory assessments, ECG, or physical examination with Fospropofol$_{FP.}$

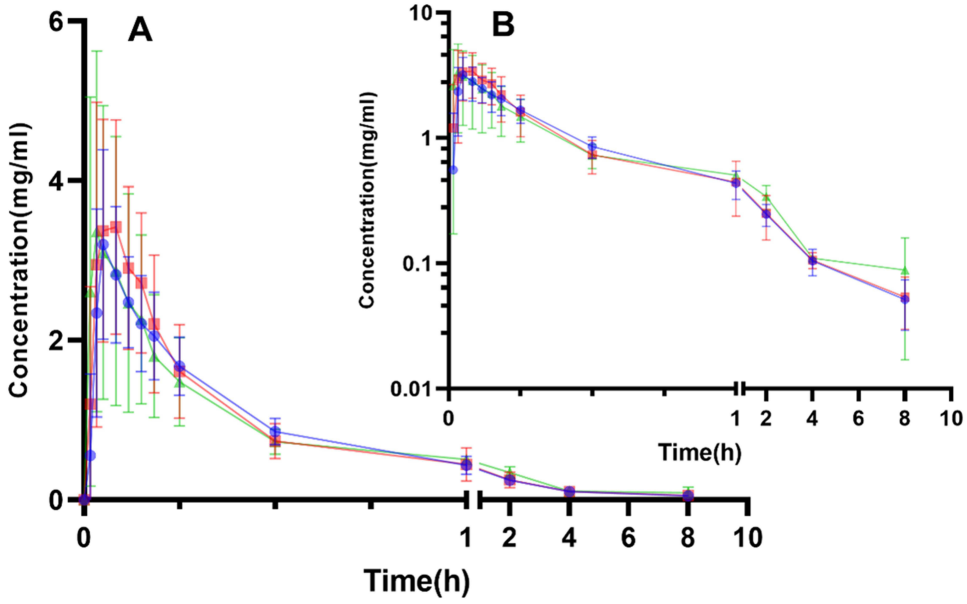

Figure 2 Propofol Plasma concentration-time profile (**A**) linear scale and (**B**) semi-log scale. Line blue: Normal Liver Function (n=10); Line Red: Moderate Liver Dysfunction (n=10); Line Green: Severe Liver Dysfunction (n=3).

Table 4 PK Parameters in Patients with Various Degrees of Hepatic Impairment (Propofol)

Index	Unit	Normal Liver Function (n=10)	Moderate Liver Dysfunction /Grade B (n=10)	Severe Liver Dysfunction /Grade C (n=3)
$AUC_{(0\rightarrow 8h)}$	h*ng/mL	2152.66±287.21	2213.65±514.80	2448.03(362.42)
$AUC_{(0\rightarrow \infty)}$	h*ng/mL	2457.65(540.48)	2640.58(557.99)	2664.41(186.53)
λz	1/h	0.28±0.09	0.27±0.07	0.29(0.11)
$T_{1/2}$	h	2.72(0.87)	2.76(0.88)	2.42(0.88)
T_{max}	h	0.05(0.05)	0.05(0.06)	0.03(0.12)
C_{max}	ng/mL	3404.00±1065.41	3810.00±1691.01	3810.00(4220.00)
MRT(0→8h)	h	1.55±0.30	1.53±0.34	1.51(1.30)
MRT (0→∞)	h	2.53(1.33)	2.48(0.81)	1.91(2.27)
Vd	L	1071.74(488.12)	1009.46(525.85)	805.57(271.94)
Cl_obs	L/h	299.34±58.38	255.55±47.90*	201.07(58.59)*

Notes: *P <0.05, compared to control group with normal liver function. Values are expressed as mean ±SD or median (Q25,Q75).
Abbreviations: AUC, area under the concentration–time curve; λz, First Order Terminal Elimination Rate Constant; $T_{1/2}$, elimination half-life; T_{max}, time of peak concentration; C_{max}, maximum concentration; MRT, mean residence time; Vd, Volume of Distribution; Cl_obs, Observed total clearance.

Univariate Analyses Between PK Parameters and Clinical Factors ($Fospropofol_{FP}$)

This univariate analysis table (Table 5) uses Spearman correlation coefficient test to explore the relationships between influencing factors and the PK parameters of $Fospropofol_{FP}$. Age shows no significant correlations with most PK parameters. Weight is significantly positively correlated with C_{max} (*$P < 0.05$). ALT, AST, and GGT are significantly or highly significantly correlated with multiple PK parameters. For example, ALT has a highly significant positive correlation with V_d (**$P < 0.01$). ALP is correlated with some parameters, such as a significant negative correlation with $MRT_{(0\rightarrow\infty)}$ (*$P < 0.05$). ALB is significantly correlated with multiple PK parameters, for instance, a highly significant positive correlation with $AUC_{(0\rightarrow\infty)}$ (***$P < 0.001$). Other indicators such as TBIL, SCr, and BUN show mostly nonsignificant correlations with all PK parameters. PT has a highly significant negative correlation with $AUC_{(0\rightarrow\infty)}$ (**$P < 0.01$).

Multivariate Analysis Using Multiple Linear Regression Analysis ($Fospropofol_{FP}$)

Multiple linear regression analysis was performed to adjust for significant correlations in the univariate analysis (Table 6). The results showed that pre-operative ALB was an independent clinical factor associated with $AUC_{(0\rightarrow\infty)}$, C_{max} and $MRT_{(0\rightarrow\infty)}$, after a single dose of intravenous $Fospropofol_{FP}$.

Table 5 Univariate Analyses Between Influencing Factors and PK Parameters ($Fospropofol_{FP}$)

Coefficients	$AUC_{(0\rightarrow\infty)}$	λ_z	$T_{1/2}$	T_{max}	C_{max}	$MRT_{(0\rightarrow\infty)}$	$Cl_{\_obs}$	V_d
Age	−0.18	0.19	−0.19	0.00	−0.12	−0.20	0.07	−0.15
Weight	0.27	−0.09	0.09	0.15	0.45*	0.09	0.11	0.33
ALT	−0.04	−0.20	0.20	0.02	0.05	0.03	0.11	0.56**
AST	−0.15	−0.01	0.01	0.06	−0.14	−0.06	0.18	0.43*
GGT	−0.51*	0.30	−0.30	0.14	−0.43*	−0.41	0.50*	0.45*
ALP	−0.38	0.32	−0.32	−0.01	−0.30	−0.42*	0.39	0.28
ALB	0.70***	−0.45*	0.45*	0.17	0.46*	0.55**	−0.52*	−0.23
TBIL	−0.38	0.32	−0.32	−0.24	−0.34	−0.27	0.20	−0.12
SCr	−0.11	−0.10	0.10	0.18	−0.19	−0.08	0.11	0.27
BUN	0.20	−0.29	0.29	0.25	−0.10	0.25	−0.26	0.08
PT	−0.54**	0.44*	−0.44*	−0.05	−0.61**	−0.32	0.39	−0.03
INR	−0.58**	0.48*	−0.48*	−0.05	−0.63**	−0.36	−0.02	0.43*

Notes: *P<0.05, **P<0.01, *** $P<0.001$,by Spearman correlation coefficient.
Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; ALP, Alkaline Phosphatase; ALB, Albumin; TBIL, total bilirubin; SCr, serum creatinine; BUN: blood urea nitrogen; PT, Prothrombin time; INR, international normalized ratio.

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Table 6 Results of Multiple Linear Regression Analysis for Clinical Factors Related to PK Parameters ($Fospropofol_{FP}$)

	Coefficient	Std. error	t value	P>t	95% CI	
$AUC_{(0\rightarrow\infty)}$						
Intercept	−34.23	25.08	−1.36	0.19	−87.13	18.68
GGT	−0.01	0.01	−1.12	0.28	−0.03	0.01
ALB	0.72	0.22	3.29	<0.01	0.26	1.18
PT	7.01	4.44	1.58	0.13	−2.35	16.37
INR	−62.92	49.44	−1.27	0.22	−167.23	41.38
λz						
Intercept	10.54	4.15	2.54	0.02	1.82	19.27
ALB	−0.06	0.04	−1.57	0.13	−0.13	0.02
PT	−1.15	0.77	−1.51	0.15	−2.76	0.45
INR	10.73	8.45	1.27	0.22	−7.02	28.48
$T_{1/2.}$						
Intercept	−0.17	0.21	−0.79	0.44	−0.61	0.28
ALB	0.00	0.00	1.62	0.12	0.00	0.01
PT	0.06	0.04	1.45	0.17	−0.03	0.14
INR	−0.51	0.43	−1.17	0.26	−1.42	0.40
Cmax						
Intercept	−178.66	134.86	−1.32	0.21	−466.11	108.79
WEIGHT	−2.61	1.51	−1.72	0.11	−5.83	0.62
BMI	10.73	6.26	1.71	0.11	−2.63	24.08
GGT	−0.02	0.04	−0.44	0.67	−0.12	0.08
ALB	3.92	1.03	3.81	<0.002	1.73	6.11
PT	10.78	21.48	0.50	0.62	−34.99	56.56
INR	−78.39	240.75	−0.33	0.75	−591.54	434.77
$MRT_{(0\rightarrow\infty)}$						
Intercept	0.09	0.07	1.30	0.21	−0.05	0.22
ALP	0.00	0.00	−0.42	0.68	0.00	0.00
ALB	0.00	0.00	2.78	0.01	0.00	0.01
Vz_obs						
Intercept	8.43	0.98	8.62	0.00	6.38	10.48
ALT	0.01	0.01	0.50	0.62	−0.02	0.04
AST	0.00	0.03	0.12	0.90	−0.05	0.06
GGT	0.00	0.00	0.59	0.56	−0.01	0.01
cl_obs						
Intercept	54.94	28.13	1.95	0.07	−3.94	113.83
GGT	0.00	0.01	0.28	0.79	−0.03	0.03
ALB	−0.64	0.33	−1.93	0.07	−1.34	0.05
INR	1.87	14.90	0.13	0.90	−29.31	33.06
Vd						
Intercept	8.44	0.98	8.62	0.00	6.39	10.49
ALT	0.01	0.01	0.50	0.62	−0.02	0.04
AST	0.00	0.03	0.12	0.90	−0.05	0.06
GGT	0.00	0.00	0.59	0.56	−0.01	0.01

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; ALP, Alkaline Phosphatase; ALB, Albumin; TBIL, total bilirubin; SCr, serum creatinine; BUN: blood urea nitrogen; PT, Prothrombin time; INR, international normalized ratio.

Table 7 Correlation Analysis of AUC (0→8h) Between Fospropofol$_{FP}$ and Propofol

	ALL	Normal Liver Function (n=10)	Moderate Liver Dysfunction /Grade B (n=10)	Severe Liver Dysfunction /Grade C (n=3)	Ratio (Relevance to the Group)
Rho	0.02	−0.03	0.62	−0.50	−0.67
P	0.92	0.93	0.06	0.48	<0.001

Notes: rho, Spearman's rank correlation coefficient; *β*, *P*-value for the Spearman correlation test; Ratio: means Fospropofol$_{FP}$ AUC/ propofol AUC.
Abbreviations: ALL, entire study population; AUC, Area under the concentration–time curve.

Table 8 Correlation Analysis on the Odds Ratio of AUC (0→8h) Between Fospropofol$_{FP}$ and Propofol

	ALL	Normal Liver Function (n=10)	Moderate Liver Dysfunction /Grade B (n=10)	Severe Liver Dysfunction /Grade C (n=3)	Ratio (Relevance to the Group)
Rho	0.01	0.16	0.59	0.50	−0.67
P	0.96	0.65	0.08	0.48	<0.001

Notes: rho, Spearman's rank correlation coefficient; *β*, *P*-value for the Spearman correlation test; Ratio means Fospropofol$_{FP}$ AUC/ propofol AUC. Ratio: means Fospropofol$_{FP}$ AUC/ propofol AUC.
Abbreviations: ALL, entire study population; AUC, Area under the concentration–time curve.

The Correlation Between AUC of Fospropofol$_{FP}$ and AUC of Propofol

To explore the PK relationship between Fospropofol$_{FP}$ and propofol, we performed a rank correlation analysis of their AUC values (Table 7) and an odds ratio-based correlation analysis (Table 8). The results indicated no statistically significant correlation between the AUC of Fospropofol$_{FP}$ and that of propofol across the three groups ($p > 0.05$). However, the ratio of Fospropofol$_{FP}$-to-propofol AUC showed a moderate negative correlation with liver injury severity (rho = −0.67, $p < 0.001$), suggesting that the ratio decreases with worsening liver function and increases with milder impairment.

Discussion

It is significant to understand the PK differences of Fospropofol$_{FP}$ in populations with various degrees of hepatic impairment. Therefore, we evaluated PK characteristics of an IV injection of 10 mg/kg Fospropofol$_{FP}$ in patients with normal hepatic function and different levels of hepatic impairment.

This study evaluated the impact of moderate and severe liver impairment on plasma exposure of Fospropofol$_{FP}$ as well as the safety of Fospropofol$_{FP}$ in individuals with moderate and severe liver impairment. The results showed that compared to healthy subjects with normal liver function, there were significant changes in the AUC of Fospropofol$_{FP}$ in patients with liver impairment. In subjects with moderate liver impairment compared to those with normal liver function, AUC decreased by approximately 43%, the C_{max} of Fospropofol$_{FP}$ reduced by 26%. The AUC of patients with severe dysfunction was significantly decreased by approximately 55%. Statistical difference in C_{max} and AUC were observed between the different groups, suggesting that Fospropofol$_{FP}$ plasma exposure may be affected by hepatic impairment. $T_{1/2}$ decreased by approximately 33%, $MRT_{(0–8h)}$, $MRT_{(0→\infty)}$) decreased by 26%, CL increased by approximately 60% in the moderate liver impairment compared to those with normal liver function. Statistical difference in $T_{1/2}$, MRT and CL were observed between the different groups, suggesting that transformation and elimination process of Fospropofol$_{FP}$ may be accelerated by hepatic impairment.

Multivariate analysis identified ALB as an independent predictor of AUC, C_{max}, and MRT, which may be related to the baseline lower albumin levels in patients with moderate and severe liver impairment. Fospropofol$_{FP}$, as a new drug, exerts anesthetic effects by converting ALP on the surface of endothelial cells into propofol (active metabolite). Liver and bone diseases are the most common causes of pathological elevation of ALP levels.[19] Hepatic ALP is present on the surface of bile duct epithelia. As functional hepatocyte mass declines (as evidenced by reduced albumin synthesis), a series of compensatory events ensue. A key event is "ductular reaction", a wound-healing response characterized by the

proliferation of bile ductules. These proliferating ductules are a rich source of ALP, leading to its increased serum levels.[20] Therefore, the decrease in ALB (marking lost hepatocyte function) and the increase in ALP (marking ductular reaction) are not directly causal but are rather parallel consequences of the same disease process: ongoing hepatic parenchymal damage and the organ's attempt to repair itself. Our multivariate analysis further supports this mechanism. ALB was a stronger predictor of drug clearance than ALP, indicating that overall loss of liver function is the main driver of pharmacokinetic changes.

Unlike traditional anesthetics such as propofol, whose pharmacokinetics largely depend on liver blood flow and cytochrome P450 enzymes,[21,22] prodrugs like $Fospropofol_{FP}$ are cleared differently, they first require hydrolysis by enzymes such as ALP.[23] To our knowledge, this is the first study to show that serum ALB strongly and independently predicts the pharmacokinetics of a prodrug anesthetic in patients with liver impairment.

Furthermore, while CL of the active metabolite propofol was significantly reduced by approximately 15% and 33% in patients with moderate-to-severe hepatic impairment compared to those with normal hepatic function, other pharmacokinetic parameters showed no statistically significant differences ($p > 0.05$). The results showed that in severe hepatic insufficiency, the pharmacokinetics of propofol were significantly affected, which may be related to the further metabolism and clearance of propofol by the liver, resulting in abnormal accumulation or clearance of propofol in the body,[24] which may further affect the overall pharmacokinetic characteristics of $Fospropofol_{FP}$.

Although patients with moderate-to-severe hepatic impairment exhibited reduced exposure for $Fospropofol_{FP}$, we observed that the loss of consciousness within 5 minutes post-administration was paradoxically higher than in those with normal liver function. This paradoxical response may be explained by an increased pharmacodynamic sensitivity to propofol in these patients, potentially compensating for the lower prodrug exposure and enhancing sedative effects. Furthermore, the higher occurrence of hypotension in the hepatic impairment group may be attributed to significantly reduced clearance of propofol, leading to its accumulation and amplified cardiovascular depressive effects. This finding is further supported by correlation analysis, which revealed a moderate negative correlation between the fospropofol-to-propofol AUC ratio and the severity of hepatic impairment. Consequently, clinicians should be aware that patients with hepatic impairment may be at increased risk for hemodynamic instability from $Fospropofol_{FP}$ due to a combination of PK accumulation and PD sensitivity, even after a single dose. Further studies in larger cohorts are warranted to confirm this relationship.

In this study, the Child-Pugh score was used to grade the liver function, which is due to its clinical relevance and practicality in perioperative settings. While the Model for End-Stage Liver Disease (MELD) score, which is calculated from serum creatinine, bilirubin, and INR, provides superior predictive accuracy for short-term mortality in end-stage liver disease,[25] In contrast, the Child-Pugh score integrates both biochemical markers (albumin, bilirubin, prothrombin time) and clinical manifestations (ascites, encephalopathy), offering a holistic assessment of chronic hepatic reserve. This approach aligns with our focus on chronic liver dysfunction (Child-Pugh B/C) rather than acute illness. Moreover, the Child-Pugh score is widely used in anesthesia research for guiding dose adjustments of hepatically metabolized drugs.[5,24,26] While the MELD score requires serum creatinine, bilirubin, and INR, involves a more complex calculation, and is less sensitive to short-term clinical changes.[27] Therefore, the Child-Pugh score was selected for this study.

Study Limitation

A key limitation of this study is the small sample size of the severe hepatic impairment group (n=3, Child-Pugh C). While this reflects real-world challenges in recruiting critically ill patients for pharmacokinetic trials, due to ethical constraints, comorbidities, and procedural risks, the limited number of participants compromises the robustness of the statistical analyses. Consequently, the findings in patients with severe liver damage should be interpreted with caution, and future studies with a larger sample size are necessary to confirm these trends and draw definitive conclusions. The Child-Pugh scale classified hepatic impairment severity. Although the most widely applied tool for this purpose, it has recognized limitations. Another limitation is the gender imbalance among the study participants with relatively few female subjects in each group. Therefore, the conclusions of this study are not fully applicable to female patients with hepatic impairment.

Conclusion

Our study is the first to report altered PK of $Fospropofol_{FP}$ in patients with moderate-to-severe hepatic impairment, report a reverse pattern of increased elimination of $Fospropofol_{FP}$ and slow elimination of the metabolite propofol, and identify ALB as an independent predictor of $Fospropofol_{FP}$'s PK. We found that the increased sensitivity in these patients may compensate for the lower exposure for $Fospropofol_{FP}$, thus not necessitating a dose change for efficacy. However, the potential for propofol accumulation necessitates further investigation into the safety of repeated dosing. Clinicians must reconcile the dual challenges of reduced prodrug bioavailability in moderate disease and metabolite accumulation in advanced cirrhosis. Future studies should integrate physiologically based PK modeling with real-world evidence from larger cohorts to optimize precision dosing in this vulnerable population.

Data Sharing Statement

All data will be made available upon reasonable request to the corresponding author.

Ethics Statement

Approved by West China Hospital Ethics Committee, No.2024551.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing financial or non-financial interests.

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