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Altered Pharmacokinetics of Fospropofol Disodium in Moderate-to-Severe Hepatic Impairment: A Prospective Controlled Study

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ABSTRACT

Fospropofol disodium for injection (Fospropofol$_{FP}$) is a recently introduced, water-soluble precursor of propofol used for procedural sedation and induction of anesthesia. This prospective cohort investigation assessed how hepatic dysfunction affects the pharmacokinetics and safety of Fospropofol$_{FP}$ during general anesthesia, comparing impaired subjects with matched healthy individuals. A total of 23 participants were recruited and grouped by liver status: normal hepatic function (n = 10), moderate impairment (n = 10), and severe impairment (n = 3). Each person received Fospropofol$_{FP}$ 10 mg/kg i.v. as a single bolus. Fourteen venous samples per subject were obtained. Concentrations of Fospropofol$_{FP}$ and its released metabolite, propofol, were quantified via LC-MS/MS. Noncompartmental analysis (NCA) using Phoenix WinNonlin was employed to derive PK metrics. Relative to healthy comparators, individuals with moderate impairment showed notably reduced exposure and faster removal of Fospropofol$_{FP}$: the AUC dropped by about 43%, while clearance increased roughly 60%. Severe impairment resulted in an AUC reduction of approximately 55%. In contrast, the active metabolite propofol displayed slower elimination, with clearance falling nearly 15% in moderate impairment and around 33% in severe impairment. Multivariate modeling indicated that preoperative albumin (ALB) independently predicted Fospropofol$_{FP}$ exposure. This study provides the first evidence that moderate-to-severe hepatic dysfunction alters Fospropofol$_{FP}$ disposition, producing the unusual combination of accelerated parent-drug elimination and delayed clearance of propofol. ALB emerged as an independent PK determinant. No unexpected safety concerns were observed after a single dose, though repeated administration warrants additional investigation.

Keywords: Hepatic impairment, Fospropofol disodium, Pharmacokinetic, Propofol, Safety

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Introduction

The liver is central to drug clearance and oversees major metabolic routes—oxidative, reductive, and conjugative—that dictate the pharmacokinetics (PK) of intravenously delivered anesthetics [1, 2]. When hepatic function declines, drug absorption, distribution, metabolism, and excretion may all shift due to alterations in blood flow, enzyme activity, and plasma-protein binding [3]. For example, ciprofol and remimazolam generally do not require dosing changes in Child-Pugh A or B conditions, but their use in Child-Pugh C patients is more carefully constrained [4, 5]. Likewise, propofol target-controlled infusion at 3 μg/mL has been associated with hemodynamic instability in advanced liver disease [6]. Even among healthy volunteers, the induction phase of anesthesia can reduce hepatic perfusion by 35–42% [7]. Consequently, PK-guided adjustments are essential for vulnerable patients.

Fospropofol$_{FP}$ (Yichang Humanwell Pharmaceutical Co., Ltd., Hubei, China) is a hydrophilic prodrug fashioned to bypass issues linked to lipid-based propofol emulsions. Once administered, it undergoes rapid enzymatic cleavage by endothelial alkaline phosphatase (ALP), releasing propofol, which produces sedation through GABA-receptor enhancement and NMDA-receptor suppression. Compared with conventional propofol, the prodrug offers a longer-lasting effect, more stable hemodynamic behavior, and avoids emulsion-related reactions [8].

Clinical trials have repeatedly shown that Fospropofol$_{FP}$ is both effective and well-tolerated for sedation and anesthesia [9–13].

Despite its increasing use, guidance for patients with hepatic dysfunction remains limited [14, 15]. No earlier work has systematically examined Fospropofol$_{FP}$ PK in Child-Pugh B or C populations or quantified the associated propofol exposure. Liver disease often elevates ALP due to cholestasis and diminishes albumin-binding capacity through reduced synthesis, structural changes, or competition with endogenous molecules. Injection mechanics—such as applied force, infusion speed, and needle characteristics—also influence tissue dispersion. Recent cadaveric and ex vivo data demonstrate that bolus versus infusion forces and needle choice can markedly alter distribution patterns [16, 17].

The present study sought to characterize Fospropofol$_{FP}$ PK in hepatic impairment to support safer anesthetic management. Our working hypothesis was that moderate-to-severe liver dysfunction could modify enzyme behavior sufficiently to hasten Fospropofol$_{FP}$ hydrolysis, consequently lowering systemic exposure and speeding its elimination.

Materials and Methods

Design

This research received approval from the Ethics Committee of West China Hospital, Sichuan University (No.2024551), where the study was also carried out. Written informed consent was obtained from every participant. The study was registered in China under the identifier CTR2400085355 and followed the principles of the Declaration of Helsinki.

A single-center, open-label, non-randomized clinical investigation using an adaptive "Reduced Design" was implemented, originally intended to progress through three sequential phases. The protocol required that pharmacokinetic differences first be examined between individuals with moderate hepatic impairment and appropriately matched healthy volunteers; evaluation of patients with mild impairment would only proceed if meaningful PK deviations were observed. Liver function categories were assigned using the Child-Pugh scoring criteria. Phase I included ten participants with moderate impairment (Child-Pugh 7–9) and ten healthy subjects matched by demographic factors. Preliminary PK assessment demonstrated less than a twofold variation in Fospropofol$_{FP}$ exposure (AUC or C_{max}) between groups, allowing Phase II to be omitted. The concluding Phase III enrolled three subjects with severe hepatic dysfunction (Child-Pugh 10–15), whose dosing was guided by PK and safety observations obtained from the moderate-impairment cohort.

Sample size justification followed established PK recommendations for hepatic impairment trials and data from comparable studies.

Participants

A total of 24 individuals scheduled for endoscopic procedures from July 2024 to December 2024 were enrolled. Screening occurred within 14 days before dosing. Inclusion criteria consisted of: ① undergoing painless endoscopy or procedures requiring quasi-general anesthesia; ② age 18–65 years, with no sex restrictions and BMI between 18–30 kg/m²; ③ liver impairment classified via the Child-Pugh system, with subjects in the normal-liver group matched by sex, age (±5 years), and BMI (±15%); ④ capacity to understand study procedures, willingness to participate, and signed consent. Exclusion criteria were: ① major comorbid conditions aside from liver disease, such as severe renal insufficiency; ② anticipated difficulty with airway management (modified Mallampati III or IV); ③ alcohol consumption within 48 hours of study participation; ④ history of substance misuse, alcoholism, or dependence on sedatives or analgesics; ⑤ previous psychiatric illness; ⑥ involvement in any drug trial during the month prior to screening; ⑦ pregnancy, breastfeeding, or refusal by men or women to use contraception during the entire study period and up to 1 month after completion; ⑧ any circumstance the investigator judged unsuitable for inclusion.

Participants were assigned to normal, moderate, or severe hepatic-impairment groups based on preoperative liver function **(Table 1)**.

Table 1. Child-Pugh Improved Grading Standard

Parameter	1 Point	2 Points	3 Points
Hepatic encephalopathy	None	Grade 1–2	Grade 3–4

Ascites	Absent	Mild (slight)	Moderate to severe
Serum total bilirubin (μmol/L)	<34.2	34.2–51.3	>51.3
Serum albumin (g/L)	≥35	28–34	<28
Prothrombin time (seconds)	≤14	15–17	≥18

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

Conduct of anesthesia

All subjects fasted for a minimum of 8 hours and refrained from liquids for at least 2 hours before the procedure. Upon entering the preparation area, two intravenous lines were placed—one dedicated to drug administration and the other for blood sampling. Continuous monitoring included ECG, noninvasive blood pressure, pulse oximetry, and bispectral index. Oxygen at 5 L/min was provided through a nasal cannula. Baseline PK samples were taken before administration, and time zero corresponded to the start of $Fospropofol_{FP}$ infusion. $Fospropofol_{FP}$ (10 mg/kg) was delivered intravenously over a 60-second period, following sufentanil 0.1 μg/kg given over the same duration to reduce discomfort.

Blood sample collection

Blood samples (4 mL) were obtained from the opposite arm and placed in K_2-EDTA anticoagulant tubes prior to dosing and at 1, 2, 3, 5, 7, 9, 11, 15, 30, 60, 120, 240, and 480 minutes after $Fospropofol_{FP}$ administration. These sampling intervals were selected to allow comprehensive characterization of the PK behavior of $Fospropofol_{FP}$ and its active metabolite, propofol, in accordance with previous literature and PK guidelines [14, 15]. Samples were centrifuged (2,000 × g, 4°C, 10 min), and the resulting plasma was transferred into primary and backup tubes (each ≥12 μL) and stored at −80°C until analysis.

Determination of drug concentration

Plasma levels of $Fospropofol_{FP}$ and its active metabolite, propofol, were quantified using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The analytical platform comprised a Shima Fluid Chromatograph integrated with a QTRAP 5500 mass spectrometer.

Pharmacokinetic analysis

Pharmacokinetic (PK) variables were derived through noncompartmental analysis (NCA) performed with WinNonlin version 8.3. Any measured concentrations falling below the quantification limit were treated as zero. Concentration–time data for $Fospropofol_{FP}$ and propofol collected from participants were used to calculate AUC(0→t), AUC(0→∞), $T_{1/2}$, clearance (CL), MRT(0→t), MRT(0→∞), and apparent distribution volume (Vd). Values for C_{max} and the corresponding T_{max} were directly extracted from the observed concentration-time profiles.

Pharmacodynamics (PD) and safety assessments

The count of subjects experiencing loss of consciousness (LOC, defined as MOAA/S < 2), the duration of LOC, and the recovery time (interval from the end of dosing until the participant was fully alert) were summarized. Safety monitoring included adverse event documentation, physical exams, vital sign measurements, clinical laboratory evaluations, and 12-lead ECGs. Each adverse event was characterized by onset, resolution time, duration, intensity, management, and clinical outcome, as well as its assessed association with the study drug. Severity grading followed CTCAE v5.0. Treatment-emergent adverse events (TEAEs) were recorded continuously over the 2-day observation window and during a telephone follow-up on day 7 after the initial $Fospropofol_{FP}$ administration.

Statistics

Plasma concentration–time plots were generated using GraphPad Prism 8.0.1. All statistical analyses were conducted in STATA 18.0, with significance defined as a P-value < 0.05. Normality of quantitative variables was evaluated via the Shapiro–Wilk test. Depending on distribution, results were expressed as mean ± SD or as median (Q25, Q75). Normally distributed data were compared using one-way ANOVA followed by Dunnett's test or the least significant difference test, whereas non-normal data were analyzed using the Kruskal–Wallis method. Due to the limited number of subjects in the severe hepatic impairment group (n = 3, Child-Pugh C), all comparisons involving this group relied on non-parametric analyses. Pearson correlation coefficients (r) were computed to

explore univariate relationships between baseline characteristics and key PK measures of Fospropofol$_{FP}$. Variables with $P < 0.05$ in univariate testing were subsequently included in multivariable modeling using multiple linear regression.

Results and Discussion

Demographics and characteristics of patients

A total of 24 participants were screened, of whom 23 were ultimately included; one was excluded due to missing data. Of these, 19 were male and 4 were female, aged 27–64 years, with body weights ranging from 49 to 89 kg. Subjects were categorized into three groups: 10 with normal hepatic function, 10 with moderate liver impairment, and 3 with severe impairment. Significant differences ($P < 0.05$) in Weight, GGT, ALB, PT, and INR were observed between the moderate/severe impairment groups and the normal-function group. Demographic and clinical laboratory information are presented in **Table 2**.

Table 2. Demographics and Laboratory Biochemical Index

Characteristic	Normal Liver Function (n = 10)	Moderate Hepatic Impairment Child-Pugh B (n = 10)	Severe Hepatic Impairment Child-Pugh 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
Body 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)
Albumin (g/L)	44.65 (2.70)	34.70 (9.35)**	30.90 (9.70)*
Total bilirubin (μmol/L)	11.54 (6.50)	32.70 (30.63)**	113.40 (137.20)*
Serum creatinine (μmol/L)	73.24 ± 15.67	78.00 ± 12.68	79.33 ± 13.65
Blood urea nitrogen (mmol/L)	5.97 ± 0.93	5.25 ± 2.13	4.60 ± 2.52
Prothrombin time (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 vs. normal hepatic function. Data shown as mean ± SD or median (IQR). Abbreviations: ALT, AST, GGT, ALP, ALB, TBIL, SCr, BUN, PT.

Pharmacokinetics of fospropofol$_{FP}$

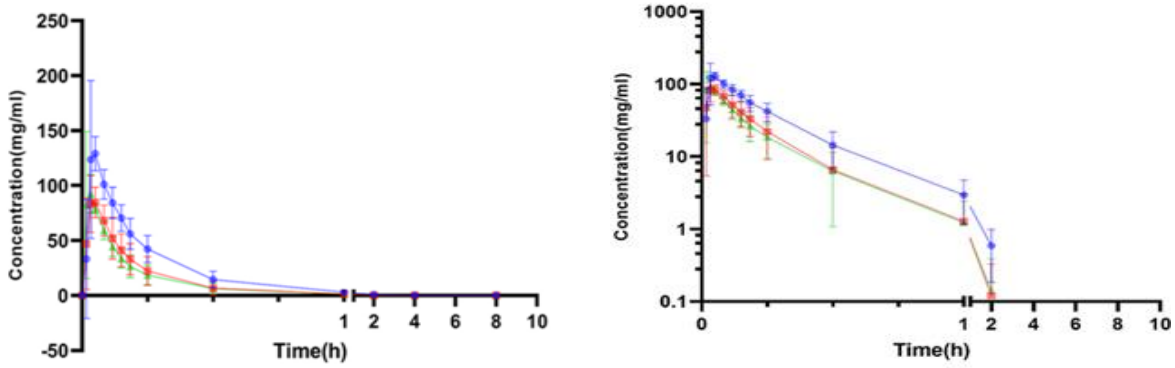
Following a single intravenous dose of 10 mg/kg Fospropofol$_{FP}$, mean concentration–time and semi-logarithmic curves for participants with normal, moderate, and severe hepatic dysfunction are illustrated in **Figure 1**. Key PK parameters are summarized in **Table 3**. Relative to subjects with normal hepatic function, those with moderate to severe impairment exhibited a more rapid decline in drug concentrations. T_{max} and V_d remained comparable among the groups, whereas AUC(0→8h) and AUC(0→∞) showed notable differences. $T_{1/2}$, C_{max}, MRT(0→8h), and MRT(0→∞) were markedly lower in the moderate impairment group compared with the normal-function group.

Table 3. PK Parameters in Patients with Various Degrees of Hepatic Impairment (FospropofolFP)

Parameter	Unit	Normal Liver Function (n = 10)	Moderate Hepatic Impairment Child-Pugh B (n = 10)	Severe Hepatic Impairment Child-Pugh C (n = 3)
AUC_{0-8h}	h·ng/mL	31,755.88 ± 8,794.45	18,132.43 ± 8,400.89**	14,396.67 (8,163.75)*
$AUC_{0-\infty}$	h·ng/mL	31,932.49 ± 8,904.74	18,254.73 ± 8,437.99**	14,521.60 (8,205.17)*
$t_{1/2}$	h	0.27 ± 0.05	0.18 ± 0.08**	0.17 (0.12)

T_{max}	h	0.04 (0.02)	0.05 (0.02)	0.03 (0.03)
C_{max}	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)
$MRT_{0-\infty}$	h	0.28 ± 0.05	0.21 ± 0.07**	0.16 (0.17)
CL_{o6s}	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 vs. normal hepatic function. Values reported as mean ± SD or median (Q25, Q75).
Abbreviations: AUC, $T_{1/2}$, Tmax, Cmax, MRT, CL_obs, V_d.



a) b)

Figure 1. $Fospropofol_{FP}$ plasma concentration–time curves: (a) linear plot and (b) semi-logarithmic plot. Blue line: normal hepatic function (n = 10); Red line: moderate liver impairment (n = 10); Green line: severe liver impairment (n = 3).

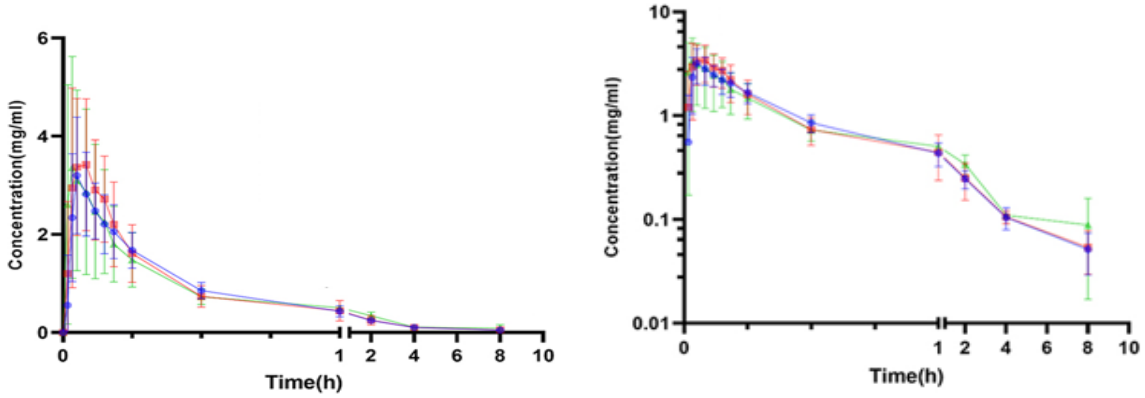
Propofol

Following a single intravenous administration of 10 mg/kg $Fospropofol_{FP}$, the mean propofol concentration-time trajectory and corresponding semi-log plot for individuals with normal, moderate, and severe hepatic dysfunction are presented in **Figure 2**. Key pharmacokinetic variables are listed in **Table 4**. Observed clearance (CL) showed a gradual reduction across groups, whereas most other PK indices remained comparable.

Table 4. PK Parameters in Patients with Different Levels of Hepatic Dysfunction (Propofol)

Parameter	Unit	Normal Liver Function (n = 10)	Moderate Hepatic Impairment Child-Pugh B (n = 10)	Severe Hepatic Impairment Child-Pugh C (n = 3)
AUC_{0-8h}	h·ng/mL	2152.66 ± 287.21	2213.65 ± 514.80	2448.03 (362.42)
$AUC_{0-\infty}$	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)
$MRT_{0-\infty}$	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_{o6s}	L/h	299.34 ± 58.38	255.55 ± 47.90*	201.07 (58.59)*

Notes: P < 0.05 vs. normal-function controls. Data expressed as mean ± SD or median (Q25, Q75).
Abbreviations: AUC; λz, terminal elimination rate constant; $T_{1/2}$; T_{max}; C_{max}; MRT; V_d; CL_obs.



a) b)

Figure 2. Propofol plasma concentration–time curves on (a) linear scale and (b) semi-log scale. Blue: normal liver function (n = 10); Red: moderate impairment (n = 10); Green: severe impairment (n = 3).

PD and safety

Loss of consciousness was observed in 5 of 10 healthy participants (50%), in all 10 subjects with moderate hepatic dysfunction (100%), and in all 3 with severe impairment (100%) after IV dosing of $Fospropofol_{FP}$ 10 mg/kg. The duration of LOC was longest in the normal-liver group (4 min) compared with the impaired groups (moderate: 2.8 min; severe: 2.7 min). Time to full recovery was similar between healthy participants (22.91 min) and the moderate-impairment group (21.09 min), but was longer among severely impaired individuals (25.51 min).

The overall safety findings were consistent across all cohorts. A slightly greater proportion of subjects in the hepatic-impairment groups reported TEAEs—4 of 10 (40%) in the moderate group and 1 of 3 (33%) in the severe group—compared with the normal group, where 3 of 10 subjects (30%) experienced two TEAEs. Paresthesia-type symptoms (pruritus, warmth, electrical or tingling sensations, or "biting" feelings) were the most frequent drug-related effects, mainly mild and occurring largely in the normal liver–function group. Hypotension (systolic < 90 mmHg or MAP < 65 mmHg for >1 min) was observed only in participants with hepatic impairment. No deaths, no serious adverse events, and no treatment discontinuations occurred. No clinically meaningful shifts were detected in laboratory values, ECGs, or physical examinations.

Univariate analyses between PK parameters and clinical factors ($Fospropofol_{FP}$)

The univariate results **(Table 5)** were derived using Spearman's correlation to assess associations between patient characteristics and $Fospropofol_{FP}$ PK variables. Age did not exhibit significant relationships with most PK outcomes. Body weight showed a significant positive correlation with C_{max} (*P < 0.05). Liver enzymes (ALT, AST, GGT) demonstrated multiple significant or highly significant associations; for example, ALT showed a strong positive relationship with V_d (**P < 0.01). ALP displayed several correlations, including a significant negative relationship with MRT(0→∞) (*P < 0.05). Albumin (ALB) was significantly associated with several PK endpoints, including a highly significant positive correlation with AUC(0→∞) (***P < 0.001). Other markers—TBIL, SCr, and BUN—had **mostly nonsignificant associations. PT demonstrated a strong negative correlation with AUC(0→∞) (**P < 0.01).**

Table 5. Univariate Associations Between Clinical Indicators and PK Indices (FospropofolFP)

Covariate	$AUC_{0-\infty}$	λz	$t_{1/2}$	T_{max}	C_{max}	$MRT_{0-\infty}$	CL_{o6s}	Vd
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
Albumin (ALB)	0.70***	−0.45*	0.45*	0.17	0.46*	0.55**	−0.52*	−0.23

Total bilirubin (TBIL)	−0.38	0.32	−0.32	−0.24	−0.34	−0.27	0.20	−0.12
Serum creatinine (SCr)	−0.11	−0.10	0.10	0.18	−0.19	−0.08	0.11	0.27
Blood urea nitrogen (BUN)	0.20	−0.29	0.29	0.25	−0.10	0.25	−0.26	0.08
Prothrombin time (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 using Spearman correlation.
Abbreviations: ALT; AST; GGT; ALP; ALB; TBIL; SCr; BUN; PT; INR.

Multivariate analysis using multiple linear regression (Fospropofol$_{FP}$)

Multiple linear regression **(Table 6)** was used to further evaluate variables that reached significance in univariate testing. Pre-treatment ALB emerged as an independent predictor of AUC(0→∞), C_{max}, and MRT(0→∞) following single IV administration of Fospropofol$_{FP}$.

Table 6. Multivariate Regression: Clinical Determinants of PK Parameters (FospropofolFP)

Parameter	Estimate (β)	Standard Error	t-statistic	p-value	95% Confidence Interval (Lower)	95% Confidence Interval (Upper)
AUC~(0→∞)						
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
λ~z~ (terminal rate constant)						
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
Terminal Half-Life (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
C~max~ (maximum concentration)						
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→∞)~ (mean residence time)						
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 (apparent volume of distribution, observed)						
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 (apparent clearance, observed)						
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 (volume of distribution)						
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; AST; GGT; ALP; ALB; TBIL; SCr; BUN; PT; INR.

The correlation between AUC of fospropofol$_{FP}$ and AUC of propofol

To investigate the pharmacokinetic linkage between Fospropofol$_{FP}$ and its metabolite propofol, we conducted a rank-based correlation of their respective AUC measurements **(Table 7)** along with an odds-ratio–oriented correlation assessment **(Table 8)**. No significant associations were detected between the AUC values of Fospropofol$_{FP}$ and propofol in any of the liver-function groups ($p > 0.05$). In contrast, the Fospropofol$_{FP}$ -to-propofol AUC ratio demonstrated a moderate inverse correlation with the degree of hepatic dysfunction (rho = −0.67, $p < 0.001$), indicating that this ratio diminishes as liver impairment becomes more severe and increases when hepatic injury is mild.

Table 7. Correlation Analysis of AUC(0→8h) Between FospropofolFP and Propofol

Parameter	All Patients (n=26)	Normal Liver Function (n=10)	Moderate Hepatic Impairment Child-Pugh B (n=10)	Severe Hepatic Impairment Child-Pugh C (n=3)	Ratio / Relevance to Reference Group	Spearman's Rho (ρ)
Value	0.02	−0.03	0.62	−0.50	−0.67	–
p-value	0.92	0.93	0.06	0.48	<0.001	–

Notes: rho = Spearman's rank coefficient; β = p-value; Ratio = Fospropofol$_{FP}$ AUC / propofol AUC.
Abbreviations: ALL, entire cohort; AUC, area under the time-concentration curve.

Table 8. Odds-Ratio–Based Correlation Analysis of AUC(0→8h) for FospropofolFP and Propofol

Parameter	All Patients (n=26)	Normal Liver Function (n=10)	Moderate Hepatic Impairment Child-Pugh B (n=10)	Severe Hepatic Impairment Child-Pugh C (n=3)	Ratio / Relevance vs Reference Group	Spearman's Correlation Coefficient (ρ)
Value	0.01	0.16	0.59	0.50	−0.67	–
p-value	0.96	0.65	0.08	0.48	<0.001	–

Notes: rho = Spearman's rank coefficient; β = p-value; Ratio = Fospropofol$_{FP}$ AUC / propofol AUC.
Abbreviations: ALL, entire cohort; AUC, area under the time-concentration curve.

Evaluating how Fospropofol$_{FP}$ behaves pharmacokinetically in patients with differing degrees of hepatic impairment is crucial. In this investigation, we characterized the PK profile of an IV dose of 10 mg/kg Fospropofol$_{FP}$ in individuals with normal liver function alongside those with moderate or severe impairment.

This trial assessed how moderate and severe hepatic dysfunction influences Fospropofol$_{FP}$ exposure and examined the drug's tolerability in these populations. When compared with subjects without liver disease, participants with hepatic impairment showed marked alterations in Fospropofol$_{FP}$ AUC values. In the moderate-impairment cohort, AUC was approximately 43% lower, and C_{max} declined by about 26%. In the severe-impairment group, AUC fell by roughly 55%. Significant differences in C_{max} and AUC across groups suggest that hepatic dysfunction substantially influences systemic exposure to Fospropofol$_{FP}$. Additionally, in the moderate-impairment group relative to the normal-function group, $T_{1/2}$ decreased by about 33%, MRT(0–8h) and MRT(0→∞) fell by 26%, and CL rose by roughly 60%. These statistically significant shifts indicate that biotransformation and elimination of Fospropofol$_{FP}$ may proceed more rapidly in the presence of impaired hepatic physiology.

Multivariate modeling identified serum albumin (ALB) as an independent determinant of AUC, C_{max}, and MRT. This likely reflects the reduced baseline ALB commonly observed in patients with moderate and severe liver disease. Fospropofol$_{FP}$, a novel anesthetic prodrug, relies on alkaline phosphatase (ALP) at endothelial surfaces for conversion to active propofol. Liver and skeletal disorders are common contributors to elevated ALP [18]. Hepatic ALP resides on bile duct epithelium; as hepatocyte mass declines—indicated by falling albumin—a compensatory "ductular reaction" occurs, marked by bile-duct proliferation. These newly formed ducts express large amounts of ALP, creating heightened serum ALP levels [19]. Thus, the decline in ALB (reflecting loss of hepatocyte synthetic function) and rise in ALP (reflecting ductular expansion) are parallel outcomes of persistent parenchymal injury rather than causally linked events. Our multivariate findings reinforce this view: ALB, more than ALP, was the principal predictor of altered drug disposition, suggesting that global hepatic dysfunction drives the PK changes seen with Fospropofol$_{FP}$.

In contrast to conventional anesthetics like propofol—whose kinetics are strongly influenced by hepatic blood flow and cytochrome P450 enzyme activity [20, 21]—prodrugs such as Fospropofol$_{FP}$ rely on enzymatic hydrolysis (e.g., via ALP) for activation and clearance [22]. To our knowledge, this study is the first to demonstrate that serum ALB is a major independent determinant of a prodrug anesthetic's PK behavior in patients with compromised liver function.

Regarding the active metabolite propofol, clearance declined by approximately 15% in moderately impaired subjects and by about 33% in severely impaired subjects compared with normal controls. Other PK variables for propofol did not differ significantly ($p > 0.05$). These data suggest that severe hepatic dysfunction meaningfully impacts propofol disposition, likely due to impaired downstream metabolism and reduced hepatic elimination capacity [23]. Such changes may, in turn, modulate the overall pharmacokinetics of Fospropofol$_{FP}$ itself.

Although patients with moderate to severe hepatic dysfunction showed lower systemic exposure to Fospropofol$_{FP}$, we found that the incidence of loss of consciousness within 5 minutes after dosing was unexpectedly higher than in individuals with normal liver function. This counterintuitive effect may stem from heightened pharmacodynamic responsiveness to propofol in liver-impaired subjects, which could offset the reduced availability of the prodrug and amplify sedative outcomes. In addition, the increased frequency of hypotensive events in the impaired-liver groups is likely linked to the markedly diminished clearance of propofol, resulting in greater accumulation and stronger cardiovascular depression. This interpretation is supported by correlation findings demonstrating a moderate inverse relationship between the Fospropofol$_{FP}$ -to-propofol AUC ratio and the degree of hepatic dysfunction. Therefore, clinicians should recognize that even a single administration of Fospropofol$_{FP}$ may predispose liver-impaired patients to hemodynamic instability due to the combined contributions of altered PK and increased PD susceptibility. Larger-scale investigations are needed to validate these observations.

In this research, the Child-Pugh grading system was employed to categorize hepatic function because of its routine clinical applicability and perioperative relevance. Although the MELD score—derived from serum creatinine, bilirubin, and INR—offers stronger predictive capability for short-term mortality in advanced liver disease [24], the Child-Pugh scale incorporates both laboratory measures (albumin, bilirubin, prothrombin time) and clinical symptoms (ascites, encephalopathy), providing a more comprehensive appraisal of chronic hepatic reserve. This better aligns with our objective of evaluating chronic liver dysfunction (Child-Pugh B/C) rather than acute deterioration. The Child-Pugh score is also widely referenced in anesthesiology literature when modifying doses of hepatically cleared medications [5, 23, 25]. Conversely, MELD requires specific laboratory values, involves more complex computation, and is less sensitive to rapid clinical changes [26]. Thus, the Child-Pugh classification was deemed most suitable for our study.

Study limitation

One major limitation is the very small number of subjects with severe hepatic dysfunction (n = 3, Child-Pugh C). This low enrollment reflects the inherent difficulties of involving critically ill individuals in PK trials—ethical issues, comorbidities, and high procedural risk—but it inevitably weakens the statistical power. Consequently, conclusions drawn from the severely impaired cohort should be regarded as preliminary, and confirmation in larger samples is essential. Although the Child-Pugh system remains the most commonly used metric for grading liver dysfunction, it is not without limitations. Another constraint is the uneven gender distribution, with relatively few female participants in each category. As a result, the findings cannot be fully generalized to female patients with hepatic impairment.

Conclusion

This work is the first to document distinct PK alterations of Fospropofol$_{FP}$ in individuals with moderate to severe hepatic dysfunction, demonstrating a paradoxical pattern in which Fospropofol$_{FP}$ clearance is accelerated while elimination of its metabolite, propofol, is slowed. We also identified ALB as an independent determinant of Fospropofol$_{FP}$ pharmacokinetics. Despite reduced exposure to the prodrug, increased pharmacodynamic sensitivity in these patients appears to sustain clinical effect without requiring dose modification for efficacy. Nevertheless, the possibility of propofol accumulation raises concerns, particularly with repeated administration, and warrants additional evaluation. Clinicians must navigate the dual issues of diminished prodrug bioavailability in moderate disease and enhanced metabolite retention in advanced cirrhosis. Future work should combine physiologically based PK modeling with data from larger real-world cohorts to refine individualized dosing strategies for this high-risk population.

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