

Simultaneous Population Pharmacokinetic–Pharmacodynamic Modeling of Fospropofol Injection (Propofol Prodrug) and Propofol Emulsion in Healthy Volunteers

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BACKGROUND

- Fospropofol disodium (Aquavan[®]) is a water-soluble prodrug of propofol developed for sedation during brief diagnostic and therapeutic procedures.
- Fospropofol is rapidly metabolized by alkaline phosphatase enzymes, releasing propofol (active moiety), phosphate, and formaldehyde. Phosphate and formaldehyde (measured as formate) do not accumulate above endogenous levels.

OBJECTIVES

- The main goal of these pharmacokinetic (PK) and PK-pharmacodynamic (PD) analyses was to compare the PK and PK-PD properties of propofol delivered from 2 different formulations: fospropofol disodium bolus dose and propofol lipid emulsion infusion (Diprivan[®]).
- Objectives of the analysis were to develop:
 - PK model of propofol concentrations in venous plasma samples following administration of a 10 mg/kg IV bolus dose of fospropofol or a 50 mg/min propofol infusion over approximately 3–4 minutes.
 - PK-PD model of the relationship between plasma concentrations of propofol and bispectral (BIS) index following administration of fospropofol or propofol.
 - PK-PD model of the relationship between venous plasma concentrations of propofol and sedation score (Modified Observer's Assessment of Alertness/Sedation [MOAA/S] score) following the administration of fospropofol or propofol.

METHODS

Study Design: Open-label, 2-period, crossover study of fospropofol versus propofol in 12 healthy volunteers (6 males, 6 females). Each subject received a single 10 mg/kg IV bolus dose of fospropofol in the first period, and the resulting maximal electroencephalogram (EEG) effect was recorded by the minimal BIS index. In the second period (after a 7-day washout), each subject received a 50 mg/min infusion of propofol (Diprivan) with varied duration intended to produce the same maximal EEG effect as observed with a dose of fospropofol.

PK Evaluation: Venous blood samples were obtained during both treatment periods at pre-dose and at 1, 4, 8, 12, 20, 30, 60, 90, 120, 180, and 240 minutes after drug administration.

PD Evaluation: MOAA/S and BIS index were assessed approximately every 2 minutes from pre-dose to 20–40 minutes post dose when all subjects returned to the fully alert state.

Assay: Samples were assayed for fospropofol by LC/MS/MS and for propofol (liberated from fospropofol or delivered by propofol emulsion) by HPLC with fluorescence detection.

Analysis Methods: A crossover design permitted intra-subject comparison of propofol PK and PD properties as a function of its delivery system, fospropofol or propofol. The goal of the population PK modeling was to describe individual propofol concentrations during sedation and for subsequent PK-PD modeling; therefore, only PK data obtained up to 70 minutes post dose were included in the analysis.

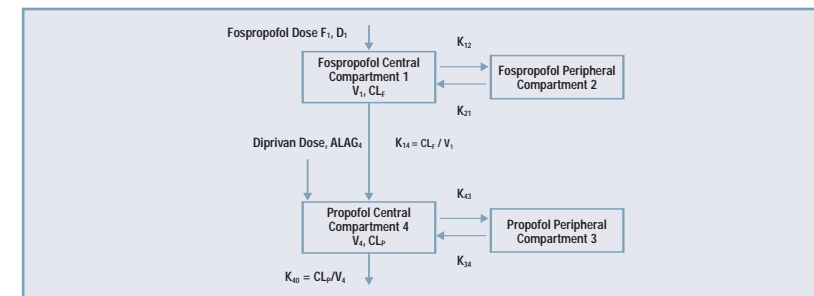
A PK model that simultaneously described both formulations was developed, and the effect of formulation on propofol clearance and volume was estimated. After the population PK model was established, individual PK parameters were used to predict propofol concentrations for the PK-PD analyses using nonlinear mixed-effects modeling with NONMEM software, Version V.

RESULTS

Population PK Model

- The population PK of fospropofol and propofol liberated from fospropofol was described by a 4-compartment linear model (Table 1).

Fospropofol–Propofol Population PK Model



A complete (100%) linear fospropofol-to-propofol metabolism was assumed.

Fospropofol and propofol models included body-size dependence via allometric scaling.

Population PK-BIS Model:

The direct sigmoid E_{MAX} model with random effects on EC_{50} and γ parameters and a formulation effect on EC_{50} adequately described dependence of the BIS index on propofol concentrations C_p (Table 2).

$$EFF = EFF_0 + (E_{MAX} - EFF_0) \frac{C_p^\gamma}{EC_{50}^\gamma + C_p^\gamma}$$

$$BIS = 100 - EFF + \epsilon_i$$

Population PK-MOAA/S Model

- Individual PK, BIS, and MOAA/S data for the representative subject are presented in Figure 1.

- A proportional odds population PK-PD model with the effect proportional to propofol plasma concentration adequately described the ordered categorical MOAA/S data for both propofol formulations (Table 3).

$$EFF = \text{Slope} \cdot C_p; A_i = B_i + EFF, i = 0, 1, 2, 3, 4;$$

$$C_i = \exp(A_i), i = 0, 1, 2, 3, 4; P_i = \frac{C_i}{1 + C_i}, i = 0, 1, 2, 3, 4.$$

Probability of a particular MOAA/S score can then be described as:

$$PR_5 = 1 - P_4; PR_4 = P_4 - P_3; PR_3 = P_3 - P_2;$$

$$PR_2 = P_2 - P_1; PR_1 = P_1 - P_0; PR_0 = P_0.$$

Expected score can be computed as:

$$ESC = 5PR_5 + 4P_4 + 3P_3 + 2P_2 + P_1.$$

TABLE 1. Population Parameters of the Fospropofol–Propofol Model

Parameter	Estimate	Bootstrap Median (95% CI)	Variability
V_1 (L)	4.58	4.36 (3.79–4.81)	
CL_F (L/min)	0.251	0.313 (0.185–0.414)	
K_{12} (1/min)	0.0364	0.0246 (0.0131–0.0531)	
K_{21} (1/min)	0.00278	0.00518 (0.00184–0.078)	
V_4 (L)	24.6	33.7 (15.1–56.1)	
CL_P (L/min)	2.01	2.45 (1.3–3.46)	
K_{43} (1/min)	0.163	0.16 (0.0955–0.233)	
K_{34} (1/min)	0.0508	0.0494 (0.0378–0.0644)	
D_1 (min)	3.3	3.32 (2.21–4.11)	
ALAG ₄ (min)	0.939	0.938 (0.895–0.962)	
$V_{4,TRT}$	0.915	0.677 (0.417–1.18)	
$CL_{P,TRT}$	1.02	0.833 (0.595–1.54)	
ω^2_{V1}	0.00396	0.00429 (0–0.0133)	CV=6.64%
ω^2_{CLF}	0.0212	0.0148 (0.00194–0.0548)	CV=16.6%
ω^2_{V4}	0.0865	0.0791 (0.00767–0.145)	CV=30.4%
ω^2_{CLP}	0.0149	0.0124 (0–0.0455)	CV=12.8%
ω^2_{D1}	0.0455	0.0429 (0–0.199)	CV=20.3%
$\sigma^2_{F,exp}$	0.00958	0.00771 (0.0037–0.011)	CV=9.81%
$\sigma^2_{P,exp}$	0.0811	0.0735 (0.0327–0.119)	CV=28.3%
$\sigma^2_{F,add 1 min}$	1080	1100 (488–2390)	SD=32.4 mcg/mL
$\sigma^2_{P,add 1 min}$	0.0225	0.0241 (0.00519–0.0778)	SD=0.156 mcg/mL

TABLE 2. Population Parameters of the Propofol-BIS Model

Parameter	Estimate	Relative SE* (%)	Bootstrap Median (95% CI)	Variability
EFF_0	4.92	13.2	4.88 (3.63–6.13)	
E_{MAX}	71.9	5.6	71.9 (67.3–91.3)	
EC_{50} (mcg/mL)	2.11	9.46	2.12 (1.84–2.9)	
γ	1.9	15	1.89 (1.4–2.4)	
$EC_{50,TRT}$	0.911	5.5	0.911 (0.822–1.03)	
ω^2_{EC50}	0.0414	31.7	0.0366 (0.0116–0.0642)	CV=20.3% (10.8–25.3%)
ω^2_γ	0.128	42.1	0.115 (0.042–0.216)	CV=35.7% (20.5–46.5%)
σ^2	44.4	17.3	43.4 (28.8–58.8)	SD=6.67 (5.37–7.67)

*SE = Standard errors

TABLE 3. Population Parameters of the Propofol-MOAA/S Model

Parameter	Estimate	Relative SE* (%)	95% CI	Variability
Slope	3.05	19.4	1.89–4.21	
B_0	-8.05	11.5	-9.87–-6.23	
$B_1 - B_0$	0.645	31.2	0.251–1.04	
$B_2 - B_1$	0.775	22.8	0.429–1.12	
$B_3 - B_2$	0.96	22.3	0.54–1.38	
$B_4 - B_3$	0.907	19.8	0.555–1.26	
$Slope_{TRT}$	1.09	6.05	0.964–1.22	
ω^2_{EMAX}	0.0745	37.8	0.0193–0.13	CV=27.3%
ω^2_{BD}	0.119	150	-0.23–0.468	CV=34.4%

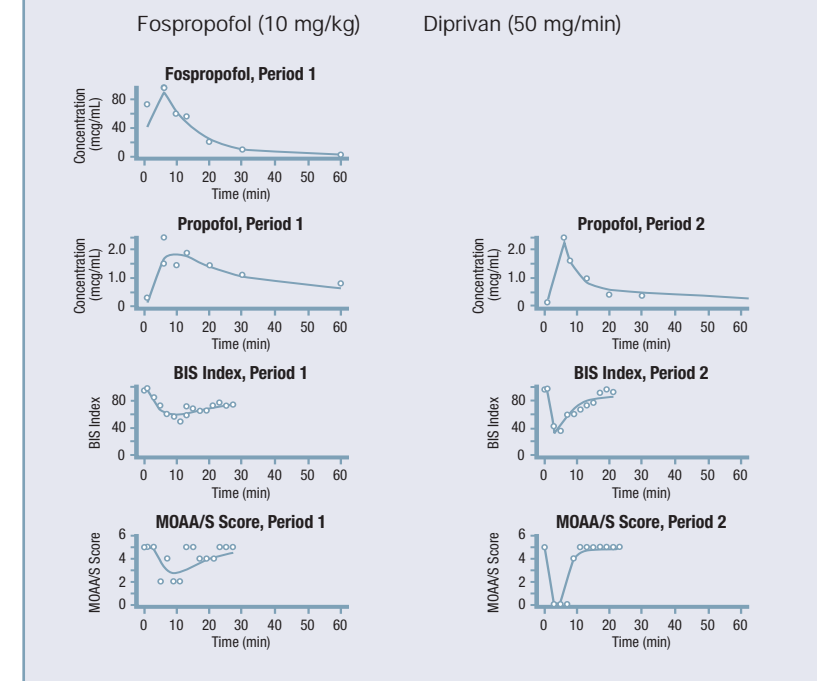
*Standard errors

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FIGURE 1. Observed and Predicted Fospropofol Concentrations, Propofol Concentrations, BIS Index Values, and MOAA/S Scores for a Representative Subject

Black circles represent observed data; lines represent individual predictions of the corresponding models



CONCLUSIONS

- The developed PK and PK-PD models adequately described fospropofol and propofol plasma concentrations, BIS index, and MOAA/S data.
- Propofol distribution and clearance were independent of the formulation, indicating complete metabolism of fospropofol to propofol.
- Effect of propofol on sedation, as measured by the BIS index or MOAA/S score, was independent of the formulation.
- The comparative PK and PK-PD (BIS) results were different than reported earlier.^{1–3} The differences may be explained by the improvement in the propofol assay methodology in the current study. Results are consistent with the non-compartmental analysis of the same study.⁴