PROPOFOL PHARMACOKINETICS ARE DIFFERENT IN A MACROEMULSION VS MICROEMULSION FORMULATION

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Summary: We investigated the effect of formulation on propofol pharmacokinetics. A novel, biosurfactant based microemulsion formulation exhibited pharmacokinetic behavior somewhat different than propofol in a lipid macroemulsion.

A novel microemulsion formulation of propofol (i.e., Aquafol®) based on "biosurfactant" technology has been developed that may address some of the lipid related problems of the current macroemulsions (e.g., Diprivan®). Changes in propofol formulation can alter its clinical behavior. The aim of this study was to compare the pharmacokinetics (PKs) of the novel microemulsion formulation with those of the most widely used lipid formulation. We hypothesized that the novel microemulsion formulation would exhibit subtle differences in its PK behavior.

Method: After approval from the Animal Care and Use Committee, 20 pigs anesthetized with isoflurane were instrumented with an intravenous catheter, a pulmonary artery catheter and a femoral artery catheter. Animals were randomly assigned to receive either the biosurfactant microemulsion (Aquafol®) or the lipid emulsion formulation (Diprivan®) of propofol by continuous infusion over 20 min at 750 mcg/kg/min. Twenty-one arterial blood samples for propofol assay were collected. Nonlinear mixed effect modeling (NONMEM®) was used to construct simple PK models for each group separately and combined. The influence of the formulation on the PK parameters was explored to construct a more complex model for the combined groups. Performance of the models was assessed graphically (e.g., individual fits, measured over predicted plots) and numerically (MDPE-median prediction error, and MDAPE-median absolute prediction error). PK simulations were used to illustrate the differences in the predicted clinical behavior of the two formulations.

Result: The shape of the concentration-time curves for both formulations was similar, although the novel microemulsion formulation exhibited a somewhat lower peak (Figure). A three compartment model was adequate to describe the PKs of both formulations. PK parameters estimated for the formulation adjusted model are shown in Table 1. Model performance was excellent. Mixed effects modeling confirmed a significant formulation effect on V2, CL1 and CL3. PK simulation using the combined model adjusted for formulation showed modest differences in the predicted concentration vs time profile after typical dosage schemes (Figure).

Conclusion: Our hypothesis was confirmed. The novel, biosurfactant based propofol formulation exhibited PK behavior somewhat different than propofol in the lipid macroemulsion. These results are consistent with a recent report in dogs[1]. These finding merit further examination in humans.

Reference:

1. Lee SH et al, Br J Pharmacol 2009; 158(8):1982-95

	Formulation Adjusted Model		
	Biosurfactant microemulsion	Lipid macroemulsion	%CV
V1 (L)	6.662	6.662	39.5
V2 (L)	8.996	7.360	23.3
V3 (L)	61.643	61.643	18.4
CL1 (L/min)	1.009	0.829	13.9
CL2 (L/min)	1.500	1.500	18.3
CL3 (L/min)	0.753	0.602	12.7
objective function	-387.255 (-368.172 for non adjusted model)		
MDPE	0.019		
MDAPE	0.109