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Determination of Plasma Protein Binding of Dalbavancin

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Background

- Dalbavancin is a semisynthetic glycopeptide with long half life, making it a promising option for treatment of *S. aureus* bacteremia.
- Free antibiotic concentration is a critical consideration in prolonged treatment courses, as free drug levels may better correlate with tissue penetration and therapeutic effect.
- Dalbavancin's protein binding has been reported between 93-99%. A reliable and validated drug assay is needed to link dalbavancin concentrations to patient outcomes.

Methods

- Ultracentrifugation was used to determine free dalbavancin concentrations in human plasma at 50 µg/mL and 200 µg/mL.

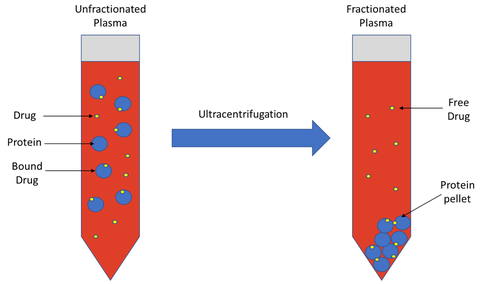

Figure 1: Ultracentrifugation Schematic

Methods (continued)

- Centrifuge tubes and pipette tips treated for 24 hours prior to use with Tween 80 to assess adsorption onto plastic.
- Centrifugation conditions: 400,000 g for 4 hours at 37°C.
- Concentrations analyzed from plasma samples (total drug) and middle layer samples (free drug) by liquid chromatography – tandem mass spectrometry (LC/MS/MS) with isotopically labeled internal standard.
- Warfarin served as a positive control with known high protein binding.

Results

- Measurement of dalbavancin was susceptible to adsorption onto plastic, however pre-treatment of tubes and pipette tips with ≥ 2% Tween 80 effectively prevented drug loss to adsorption (**Figure 2**).

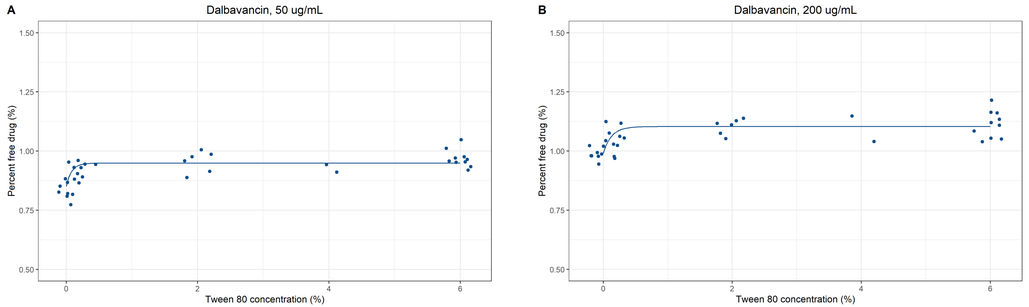

Figure 2: Percent Free Dalbavancin vs Varying Concentrations of Tween 80 for Pretreatment of Tubes

Results (continued)

- In plasma binding experiments with 2% Tween coated tubes, the free fraction of dalbavancin was 0.95% (95% CI: 0.94-0.98) at 50 µg/mL and 1.11% (95% CI: 1.08-1.13) at 200 µg/mL.
- With the ultracentrifugation method in human plasma, dalbavancin's protein binding was higher than has been observed in prior studies (**Table 1**).

Reference	Methods	Plasma Source	Reported dalbavancin Protein Binding (%)
Current study	Ultracentrifugation	Human	~99%
Andes and Craig *Antimicrob Ag Chemother* 2007	Ultrafiltration	Mouse	98.4%
Candiani et al *J Antimicrob Ag Chemother* 1999	Isothermal titration micro-colorimetry	Rat	>98%
Dorr et al *J Antimicrob Ag Chemother* 2005	Not available (abstract only)	Not available (abstract only)	93-95%

Table 1: Comparison to Existing Dalbavancin Protein Binding Data

Conclusions

- By ultracentrifugation method, dalbavancin showed ~99% protein binding.
- Given dalbavancin's high protein binding, accurate measurement of free concentration should be an important consideration in future exposure-response studies/trials.
- Future investigations should determine if active fraction is best predicted by free or total fraction.

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