Therapeutic Drug Monitoring in Interstitial Fluid: a Feasibility Study Using a Comprehensive Panel of Drugs

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Poster #30

Introduction

•Therapeutic drug monitoring (TDM) usually requires drawing blood.
•Obtaining blood samples might be difficult in certain populations such as neonates, infants, children, and patients with fragile/bad veins.
•Interstitial fluid (ISF) can serve as an alternative matrix for TDM in patients for whom it has traditionally been impossible to draw sufficient blood samples.
•ISF is essentially equivalent to blood without the proteins and has the following potential advantages:

- Minimally invasive
- Minimally painful
- No bleeding
- Hemolysis of no concern
- Direct analysis possible without cleanup

•The **objective** of this study was to determine the feasibility of using ISF for TDM by comparing concentration-time profiles in ISF and blood using a panel of drugs that warrant TDM in the clinic today. A **novel scoring algorithm** was also devised to help aid the determination of the suitability of using ISF for TDM.

Methods

•An ultrafiltration probe (UF-3-12, Bioanalytical Systems Inc) for ISF collection was implanted SC between the shoulders of rabbits (n = 4 – 6 / group).
•On the next day, an IV bolus of vancomycin (20 mg/kg), gentamicin (50 mg/kg), tacrolimus (0.1 mg/kg), cyclosporine (5 mg/kg), mycophenolate (40 mg/kg), valproic acid (50 mg/kg), phenobarbital (30 mg/kg), phenytoin (10 mg/kg), carboplatin (18.7 mg/kg), cisplatin (3 mg/kg), methotrexate (15 mg/kg), theophylline (12 mg/kg), or digoxin (0.02 mg/kg) was administered into the ear vein.
•Serial (0 – 72 hrs post dose) of ISF and blood concentrations were determined by validated drug assays.
•Pharmacokinetic parameters were generated using Phoenix™ WinNonlin 5.1.

Figure 1: Scoring Algorithm to Determine the Feasibility of TDM in ISF

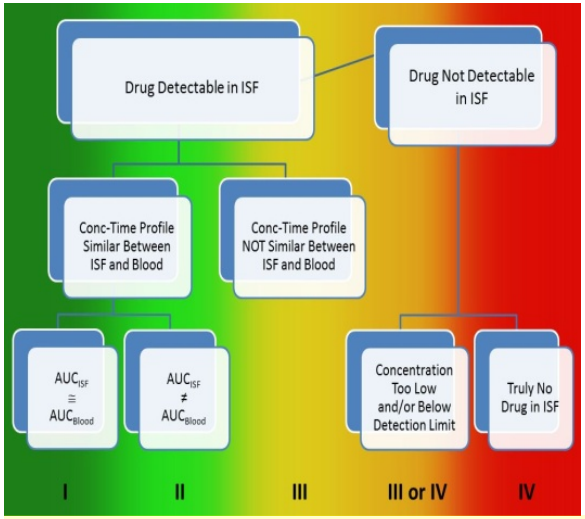
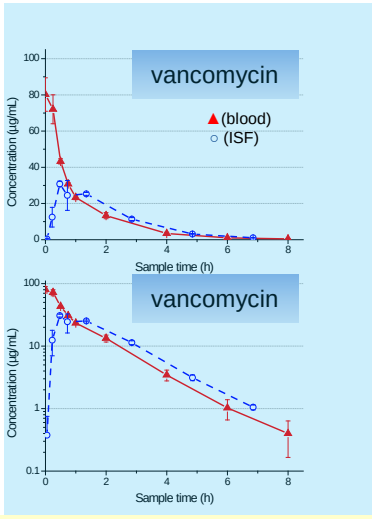


Figure 2: Concentration-Time Profiles



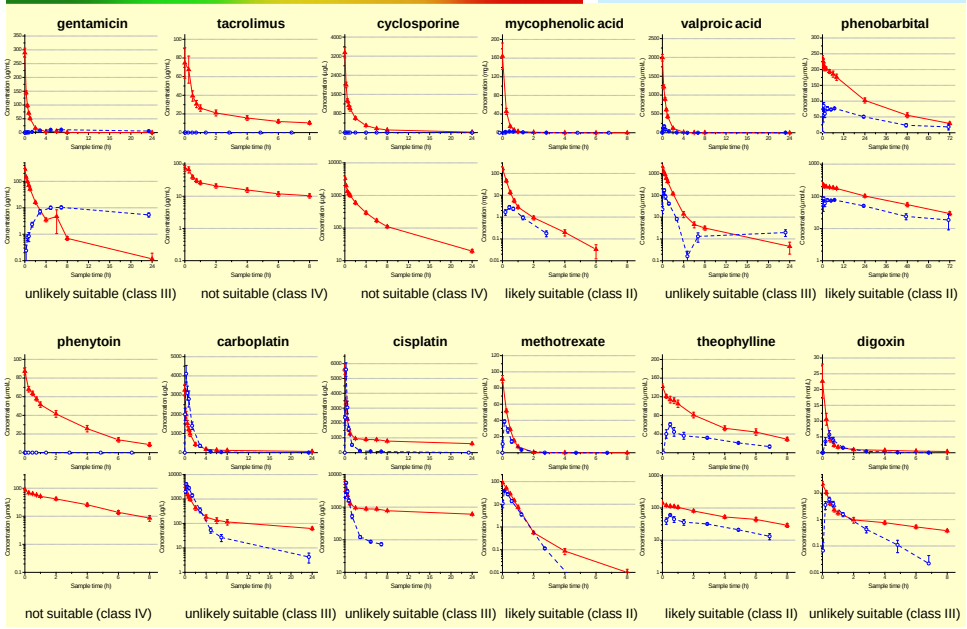


Table 1: Cmax and AUC Values (ISF vs. Blood)

*p < 0.05

Drug	Cmax		AUC	
	ISF	Blood	ISF	Blood
vancomycin (µg/mL)	32.1 ± 2.6*	80.2 ± 18.5	75.3 ± 7.7	89.8 ± 15.7
gentamicin (µg/mL)	10.8 ± 3.6*	289.5 ± 40.3	176.1 ± 54.0	188.8 ± 44.7
tacrolimus (µg/mL)	ND	74.7 ±32.8	ND	157.3 ± 48.7
cyclosporine (µg/L)	ND	3349.2 ± 536.9	ND	5144.4 ± 1129.5
mycophenolic acid (mg/L)	2.6 ± 1.3*	164.2 ± 69.3	3.2 ± 1.3*	40.3 ± 15.9
valproic acid (µmol/L)	178.2 ± 56.6*	1992.5 ± 217.6	177.5 ± 32.5*	1424.9 ± 213.3
phenobarbital (µmol/L)	95.6 ± 16.8*	239.3 ± 20.1	2822.4 ± 274.5*	6700.4 ± 1199.2
phenytoin (µmol/L)	ND	87.4 ± 8.7	ND	241.4 ± 49.3
carboplatin (µg/L)	4110.5 ± 1058.9	3259.3 ± 730.1	5667.3 ± 1755.6	5004.1 ± 2049.9
cisplatin (µg/L)	5600.0 ± 1017.1	5639.0 ± 799.9	4002.3 ± 826.7*	20128.1 ± 1328.1
methotrexate (µmol/L)	36.3 ± 8.7*	90.8 ± 10.9	19.7 ± 5.2*	39.4 ± 5.2
theophylline (µmol/L)	62.6 ± 7.1*	142.5 ± 12.4	190.8 ± 51.8*	513.9 ± 103.7
digoxin (nmol/L)	5.9 ± 2.9*	22.7 ± 13.2	6.4 ± 3.2*	14.6 ± 6.9

Conclusion & Future Direction

•A novel scoring algorithm for determining the feasibility of using ISF for TDM has been devised (Fig 1).
•Vancomycin is **suitable** for TDM in ISF (Fig 2, Table 1).
•Other drugs can be classified as **likely suitable, unlikely suitable,** or **not suitable** (See Fig 1 for the suitability grading of individual drugs)
•Clinical studies to determine the feasibility of ISF for TDM are being planned for select drugs.

Acknowledgements

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