In-use Variability of Tacrolimus Concentration in Compounded Suspension for Transplanted Pediatric Patients

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Background

Variations of drug concentrations of oral compounded preparations may affect drug safety and efficacy (inaccurate dosing, altered absorption, potential contamination, etc.)

- Significant impact for narrow therapeutic index drugs
- Limited stability data and guidance on the storage condition of drugs

Tacrolimus: first-line immunosuppressive agent for the prophylaxis of organ rejection in patients receiving solid organ transplant and for the treatment of refractory rejection in liver or kidney transplants

- Only available as capsules in Canada (no marketed pediatric formulation)
- Compounding is needed for young children unable to swallow

Suspicion that real-life use may impact the quality of the compounded formulation and variability of tacrolimus PK profile

Objectives

Primary:

- To measure concentrations in bottles of tacrolimus compounded suspension (TCS) stored and handled according to various scenarios mimicking real-world use and to compare with the expected concentration (0,5 mg/ml ± 10%)

Secondary:

- To evaluate presence of microbial contamination after 56 days
- To determine the relevance of conducting a complete study of TCS variability in real-world use by pediatric transplanted patients, as this experimental study serves as a pilot project

Methodology

Simulation of a pediatric transplanted patient (14 kg):

- **Tacrolimus 0.15 mg/kg/day – TCS 0.5 mg/ml 2 ml PO BID for 28 days** (first pouring the amount into a 30 mL measuring cup and then withdrawing 2 mL using a 3 mL syringe)
- Stability of TCS according to available data: 56 days
- Possible concomitant use of amlodipine in some scenarios: 1ml of amlodipine 1 mg/ml withdrawn in the syringe and put back in its bottle prior to tacrolimus sampling with the contaminated syringe.

9 bottles of TCS (150 ml – 0.5 mg/ml) were prepared by hospital pharmacy (Table 1)
Validated ultraviolet high-performance liquid chromatography for concentration assay
Microbial analysis after 14 days on agar for bacterial and fungal growth

Table 1. Handling conditions of bottles of TCS 0.5 mg/ml

Bottle	Specific conditions	Temp. (°C)	UV exposure	Agitation for 30 seconds	Amlodipine contamination	Amber bottle
Control						
1	No manipulation between days 0-56[1]	2-8		x		x
Simulated in-use scenarios with twice daily 2 ml sampling[2]						
2	Ideal in-use conditions	2-8		x		x
3		2-8				x
4		2-8		x	x	x
5		2-8			x	x
6		20-25	x	x		x
7	Clear bottle	20-25	x	x		
Other scenarios						
8	Freezing effect[3]	-20				x
9	Bottle bottom effect[4]	20-25		x		x

[1]Subsequent analysis after expiration (days 56-84)
[2]The 2 ml sample was either discarded or used for HPLC assay on pre-determined days (day 0 and every 7 days) as two 1 ml aliquots transferred into two 5 ml cryovials and stored in a freezer at -80°C
[3]HPLC assay was conducted 24 hour after freezing
[4]Bottle shaken 30 seconds on first sampling only (for baseline concentration). 14 samples taken each day until the bottom of the bottle is reached (day 4)

Results

- Stability of control bottle (#1) did not exceed the expected ±10% variation from D0 to D84 (range -8% to -3%) with initial concentration = 0.475 mg/ml (-5%)
- 4 out of 9 bottles had borderline baseline concentrations of 0.45 mg/ml (-10%)
- Of the 6 bottles sampled twice daily over 28 days, 4 were below 0,45 mg/ml on day 7. 5 bottles were below 0.45 mg/ml on days 14, 21 and 28
  - Bottle #7 was the most affected (direct exposure to daylight) with a variation of -33% from baseline concentration (and -31% from expected 0.5 mg/ml)
- No significant freezing effect (bottle #8) or no apparent bottle bottom effect (bottle #9)
- No microbial growth detected up to day 56

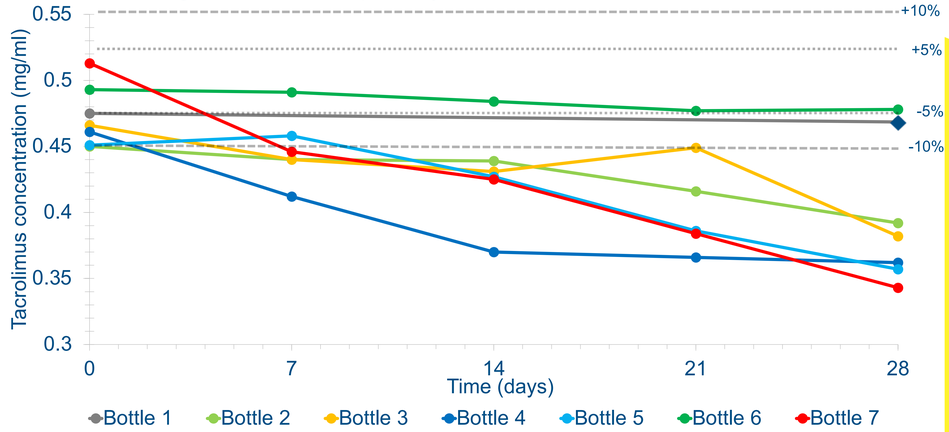

Figure 1. Concentration of TCS over time for bottles #1 to 7

◆ Data extrapolated from day 56 concentration assuming linear regression

Conclusion

Oral drug compounding has many limitations over commercially available products. In this pilot study, there is noticeable variability in preparation and stability of 9 TCS bottles in controlled in-use conditions. This should be considered by clinicians in their evaluation of patients with a suboptimal response to a compounded medication. A real-world study of TCS administered to transplanted pediatric patients is highly relevant and may translate into identifying significant handling conditions.

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