CURRENT VANCOMYCIN DOSING RECOMMENDATIONS FOR PEDIATRIC PATIENTS: A PHARMACOKINETIC EVALUATION

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Introduction

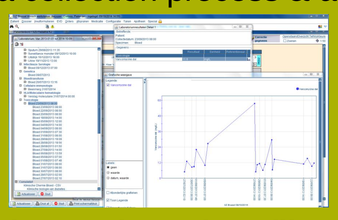
Current vancomycin (VANC) dosing schemes for children recommend using 40 - 60mg/kg bodyweight/day, divided in3-4 doses and adjusted afterwards according plasma trough levels. From local observations in our own hospital and literature, multiple dose escalations over several days after start of therapy are often needed to obtain adequate plasma levels. Such delay may compromise clinical outcome, in particular for patients with sepsis and/or immunosuppression.

Objective

To evaluate the currently used dosing scheme in our hospital (15 mg/kg, 4 times daily) against the optimal PK/PD parameter for VANC of AUC/MIC≥400 and the recommended plasma trough levels (10-20mg/L).

Methods

- Setting: retrospective study on pediatric ward with a large proportion of hematological patients, in a tertiary care university hospital, Brussels, Belgium.
- Inclusion criteria: patients >1 year and <18 years, who received VANC between 2011 and 2013 in intermittent infusion with at least 4 consecutive doses.
- Exclusion criteria: patients on intensive care, continuous VANC infusion, <4 doses given or no serum creatinin or VANC levels available
- Data collection process & analysis:



Electronic patient files:
- ***VANC dose & frequency***
- ***Infusion time***
- ***Trough levels***

JPKD v3.1 JavaPK for Desktop

Settings:
- ***1-compartment***
- ***1st order***
- ***Bayesian analysis***

Individual PK parameters (clearance, Vd, AUC)

MS Access database

Adding patient variables:
- ***age, gender, body weight, length***
- ***diagnosis, comorbidities***
- ***Creatinin clearance, administered fluids, (nephrotoxic) co-medication***

Statistical analysis SPSS 22.0

- The Minimum Inhibitory Concentration (MIC) was set to a conservative value of 1mg/L.
- For analysis, patients were stratified according age: <6 years, 6-12 years and >12 years.
- All doses are expressed to be given 4 times daily.

Outcomes

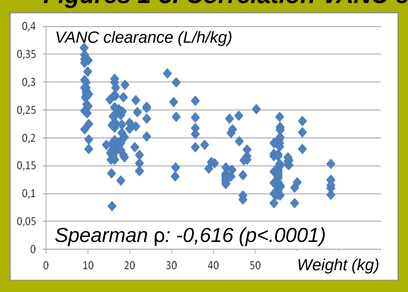
- Twenty-four patients included with 183 available trough levels.

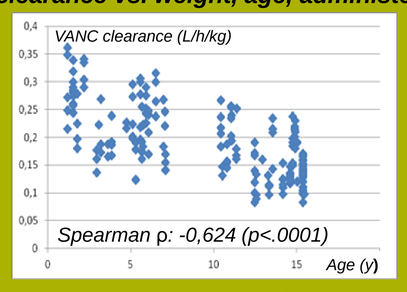
Table 1. Patient characteristics

Patient variables (N=24)	Median (interquartile range)
Age (year)	6.3 (range 1 - 15)
Gender (male/female)	15/9
Hematological/oncological malignancy	21
Body weight (kg)	19.98 (16.35 - 43.00)
Length (cm)	114.50 (102.60 - 156.00)
Serum creatinin (mg/dL)	0.38 (0.30 - 0.45)
VANC trough level (mg/L)	10.13 (7.14 - 13.54)
Vancomycin clearance (L/hr/kg)	0.186 (0.14 - 0.24)
Creatinin clearance (ml/min/1,73m²)	195.08 (156.58 - 244.44)
VANC distribution volume (L/kg)	1.08 (1.06 - 1.11)

- VANC clearance was significantly correlated with:
  - ✓ Body weight
  - ✓ Age
  - ✓ Administered fluids

Figures 1-3. Correlation VANC clearance vs. weight, age, administered fluids





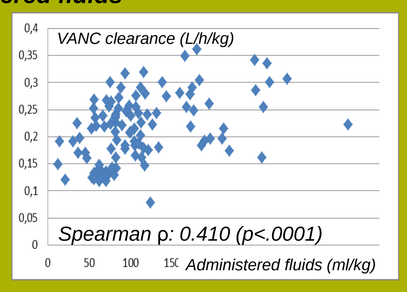


Table 2. Overview PK parameters for different age strata

Age (years)	Number of patients	Median VANC clearance (L/h/kg)	Median dose (mg/kg)	Median trough (mg/L)
< 6	9	0.2260	24.31	9.89
6 -12	11	0.2071	18.38	10.55
> 12	4	0.1350	13.95	11.41

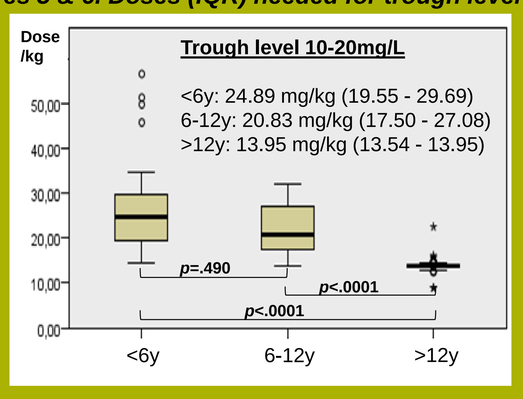
- 44,8% of trough levels was inadequate. Agreement between adequate trough levels and appropriate AUC/MIC was 86.0% (Positive Predictive Value: 80%).

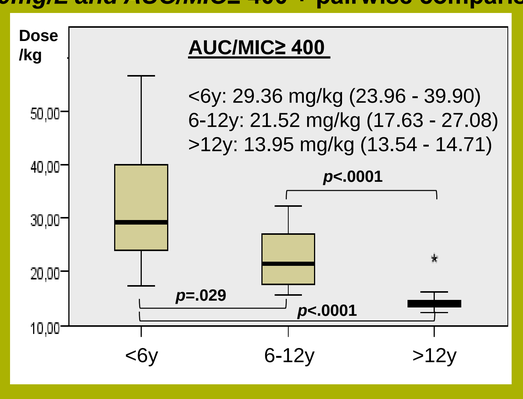
Table 3. Relation trough levels – AUC/MIC

AUC/MIC	Trough level (mg/L)		
	< 10	10 - 20	> 20
< 400	85.4% (70)	**14.0% (13)**	0% (0)
≥ 400	14.6% (12)	**86.0% (80)**	100% (8)

- To obtain AUC/MIC≥400 and adequate trough levels (10 - 20mg/L) dose ranges were comparable and in both cases highly significantly different (Kruskal-Wallis: 65.75 and 61.26 resp.; both *p*<.0001).

Figures 5 & 6. Doses (IQR) needed for trough level 10-20mg/L and AUC/MIC≥ 400 + pairwise comparisons





- The impact of a hematological/oncological malignancy on VANC dosing is unclear in our patient population but cannot be ruled out.

Table 4. Dose needed for AUC/MIC ≥ 400 with hematological/oncological comorbidity

	Malignancy	No malignancy	*p*-value
Median dose (mg/kg; IQR) needed for AUC/MIC≥ 400	21.63 (15.62 - 29.53)	18.12 (14.71 - 21.52)	Mann-Whitney *p*=.735 Wald-Wolfowitz *p*=.002

Conclusion

- Current vancomycin dosing recommendations are clearly insufficient for all pediatric patients and should be more tailored according patient's age.
- Other potentially important factors that should be considered to further guide vancomycin dose regimens are body weight, volume of administered fluids and the presence of a hematological/oncological malignancy.
- In order to quickly obtain adequate levels, the following initial dosing scheme should be considered, especially for hematology/oncology patients: <6 years: 4 x 25-30 mg/kg/day; 6-12 years: 4 x 20 mg/kg/day; >12 years: 4 x 15 mg/kg/day, with subsequent dose adaptations according trough levels. A larger prospective study will be needed to confirm the optimal dose regimens for vancomycin for different pediatric patient populations.