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Vancomycin administered by continuous infusion should be dosed according to clearance and not according to patient's body weight

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1. Introduction

Continuous infusion (CI) of vancomcyin is gaining increasing popularity because of facilitated therapeutic drug monitoring and nursing [1].

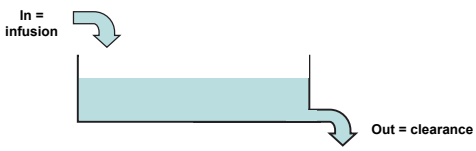
In a recent Belgian survey [2], however, we observed that several recommendations for CI of vancomycin indicate a dosing as "mg per kg of body weight" during the infusion, based on literature data [4,5].

Pharmacokinetic considerations, however, show that serum level during CI (after reaching the desired value by administration of a loading dose) is only dependent of the drug infusion rate and of its clearance (CL) according to the formula:

$$C_{ss} = K_o/CL \quad \text{(eqn.1)}$$

were C_{ss} is the steady state serum concentration, K_o the infusion rate (supposed to be constant) and CL the drug clearance).

This is illustrated by the following cartoon:



Once a bath is at the desired level (i.e. after the loading dose), maintaining its level constant does not depend upon its volume but of the ratio of tap and drain flows (which must be equal: in = out...)

Vancomycin clearance, however, is often deduced from the calculated creatinine clearance (CCrCL) value [5] which is obtained using the Cockcroft-Gault formula (CGF)

CCrCL = ((140-age) x weight / (Pl. creat. x 72)) x F (eqn. 2)

This formula includes weight as one of its key parameter. One might, therefore, erroneously believe that the final dosage is correctly expressed as mg/kg.

2. Objectives

To explain why vancomycin administered by CI must be administered on the basis of its clearance **only** and **not as mg per kg of body weight** (even if corrections are made for clearance using CGF) and how using mg/kg for dosing during the CI leads to errors.

3. Methods

Using the parameters of an ideal risk-factor free patient (age = 45 y; plasma creatinine = 1 mg/dL; male [F=1]) we ran 3 simulations showing

- how CCrCl varies as function of body weight in the CGF:

  CCrCL = 95 x weight / (1 x 72) (eqn. 3 [from eqn. 2])

- how vancomycin Css varies as a function of CCrCL:

  $C_{ss} = K_o$ / (0.65 x CCrCL) (eqn. 4 [from eqn. 1 and ref. 5])

- how vancomycin C_{ss} also varies as function of the body weight included in the CGF:

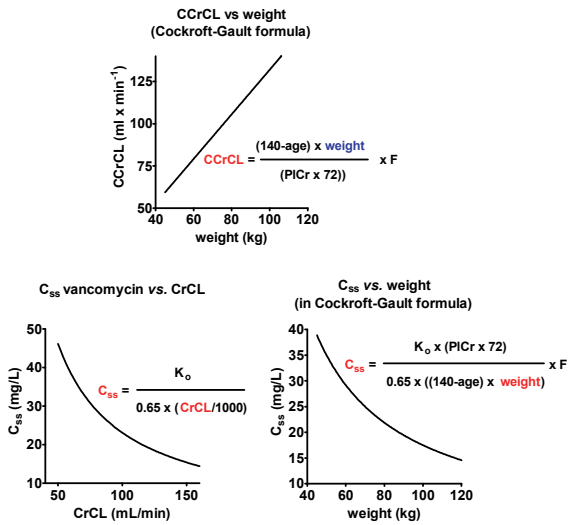
  $C_{ss} = (K_o$ x (1 x 72)) / (0.65 x 95 x weight) (eqn. 5 [from eqns 3-4)

We then calculated actual vancomycin C_{ss} for patients with increasing body weight but similar CCrCL and dosed as mg/kg body weight.

4. Results

The 3 simulations presented in the Figure show that

- while CCrCL and weight are linearly related in the CGF;
- C_{ss} is **NOT** linearly related to CCrCL and is also **NOT** linearly related to weight as included in the CGF because both parameters appear in the denominator of the corresponding equations.



The Table shows that dosing by weight (mg/kg) patients with identical CCrCL but with different body weights results in markedly different C_{ss}, which is not what is anticipated.

Patient's weight (kg)	Patient's CCL (ml/min)	daily dose as mg/kg [1]	total daily dose in 24h (mg)	C_{ss} [2] (mg/L)
50	100	30	1500	**16.03**
60	100	30	1800	**19.23**
70	100	30	2100	**22.44**
80	100	30	2400	**25.64**

[1] as most often recommended in the literature (e.g., refs 2-4) for daily dose during the continuous infusion

[2] calculated according to equation 1 (introduction) and using a correction factor of 0.65 (commonly accepted ratio of vancomycin to creatinine clearance [5])

4. Conclusions

- Contrary to several recommendations, vancomycin dosing for CI after administration of a loading dose should NOT be made as "mg/kg body weight" but rather as inverse function of its clearance.
- Corrections for abnormal clearances must be made by adjusting the rate of infusion, even if clearance is calculated using the CGF and, therefore, introduces the boy weight (this is all the more essential since the body weight used in CGF should be the ideal or adjusted body weight and not total weight for best prediction of CrCL)

Note: this does not apply to the loading dose which must be administered based on the expected volume of distribution of the drug (e.g., 0.7-9 L/kg for vancomycin).

References

[1] Van Herendael *et al*. Ann Intensive Care. 2012; 2:22
[2] Buyle *et al*. Eur. J. Clin. Microb. Inf. Dis. 2013 (in press);
[3] Wisocki *et al*. Antimicrob Agents Chemother. 2001; 45:2460-7.
[4] Roberts *et al*. Antimicrob Agents Chemother. 2011; 55:2704-9
[5] Moellering *et al*. Ann Intern Med 1981; 94:343-346

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