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Vancomycin Administered by Continuous Infusion Should Be Dosed According to Clearance and Not Based on Patient's Body Weight

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Background and Aims

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

In a literature survey, we observed that authors often dose of vancomycin in "*mg per kg of body weight*" during the infusion [see e.g. 2,3], which seems to be widely used by clinicians [4].

Yet, simple pharmacokinetic considerations (see hereunder) tell that the dosage of a drug administered by continuous infusion should only be dependent of its clearance and not to weight during the infusion.

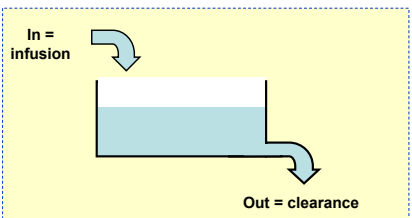
We therefore contacted the authors who mentioned that they based their recommendations on the fact that vancomycin clearance was most often not measured but calculated, using the Cockroft & Gault formula (CGF) that contains weight as one of its parameter.

The aim of this poster is to show that patient's weight shoud not be used when calculating vancomycin dosage during the infusion even if using the Cockroft & Gault's formula, as this would cause a major dosage error resulting in grossly inappropriate serum levels.

Concepts

Qualitative

The aim of continuous infusion of vancomycin is to maintain its serum level at a fixed value. This is similar to maintaining the level of water constant in a bath where water flows in through the tap (= drug infusion) and flows out through the drain (= drug clearance). In such situation, the level of water, once the bath has been filled up to the desired level, is only dependent upon the ratio of "in" and "out" flows (infusion and clearance) and the size of the bath (= patient's body weight) is unimportant.



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...)

Quantitative

The serum level of a drug during infusion is given by the following 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).

The calculated creatinine clearance according to CGF is:

$$CC_rCl = ((140\text{-age}) \times \text{weight}) / (Pl.creat. \times 72)) \times F \quad \text{(eqn. 2)}$$

were Pl.creat. is the plasma concentration of creatinine and F a correction sex factor (F=1 for males).

The serum level calculated from combining the two equations is now:

$$C_{ss} = K_o \times Pl.creat \times 72 \times F / ((140\text{-age}) \times \text{weight}) \quad \text{(eqn. 3)}$$

Since the daily dose is K_o x time, dividing it by the weight would cause Css to be multiplied by weight, which is what creates the error.

References

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6. Ampe *et al.* Int J Antimicrob Agents 2013 May;41(5):439-46 – PMID: 23523733

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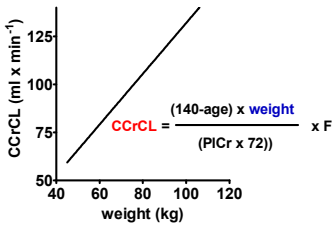
Modeling

We performed 3 simulations showing that

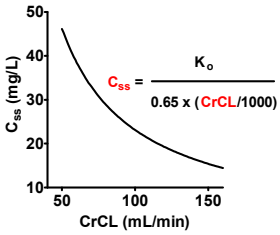
1. the calculated creatinine clearance (CC_rCL) is linearly **linearly** related to the patient's weight (**1**);
2. but that the serum level of vancomycin[a] during infusion is **NOT** linearly related to CC_rCL (**2a**) and is also **NOT** linearly related to weight as included in the CGF (**2b**) because weight appears in the denominator (thus weight corrections in (1) and (2) are different and cannot be mixed);
3. using a "dose per kg" rather than a "dose by clearance" results in different serum levels for patient with identical clearance (**3**), leading to suboptimal serum levels in lean patients (as shown) or too high levels for overweight patients (not shown).

[a] using a correction factor of 0.65 for correlation between vancomycin and creatinine clearance [5]

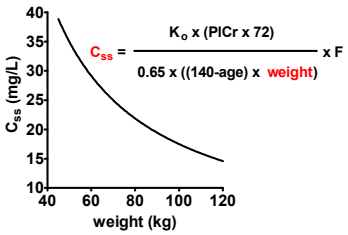
1 CCrCL vs weight (Cockroft-Gault formula)



2a C_{ss} vancomycin *vs.* CrCL



2b C_{ss} *vs.* weight (in Cockroft-Gault formula)



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Patient's weight (kg)	Patient's CC,L (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** [3]

[1] as most often but erroneously recommended in the literature (e.g., refs 2-4) for daily dose during the continuous infusion
[2] calculated according to equation 1 and using a correction factor of 0.65 (commonly accepted ratio of vancomycin to creatinine clearance [5])
[3] recommended serum level to cover organisms with an MIC up to 1.5 mg/L (see [6])

Discussion and Recommendations

Dosing vancomycin by weight (mg/kg) during continuous infusion is a mistake as it leads to incorrect values if patients deviate from ideal body weight.

Clinicians wishing to use vancomycin by continuous infusion should

- administer first a loading dose calculated on the basis of body weight (typically 20 mg/kg over 1h for normal V_d);
- then start the infusion and adjust their dose on the basis of clearance only (typically 11 mg/h for CC_rCl of 0.1L/h)

Practical recommendations are available from ref. [6] and from our web site (*http://www.facm.ucl.ac.be/vancomycin*)

With approval from the Belgian Common Health Care Ethical Platform (visa no. 13/V1/4806/052017)

A copy of this poster will be available after the meeting at http://www.facm.ucl.ac.be/posters