

# Case presentation



**SHPHK MEETING**

**Sept 2013**

# Pharmacokinetics of vancomycin in paediatric patients



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- Patient VD
- 7 yr old female
- Admitted to general ward for fever x 3 days, chills abdominal pain, vomited x 2, TOCC –ve
- On admission: on-off fever, well perfused, throat congested, chest CXR clear, abd soft
- Lab: WBC 9.57, ANC 0.97, platelet 157, NPS –ve, RFT 57 [SCr]; 3.4 [Urea]



- Lab (cont.): urine multistix –ve
- Fever: max 38.7 C
- Started on po Augmentin
- CRP elevated -> 104, WBC 9.21, ANC 6.41
- Continue to have fever
- Changed to IV Augmentin 30mg/kg q8h
- D3 of admission : c/o R knee pain



- No previous trauma / injury, minimal swelling with full ROM → ? muscle pain
- Blood culture taken
- Investigated further for septic arthritis → RF, Anti-nuclear antibodies
- CRP cont elevated to 186, WBC 15.5, ANC 12.09, ESR > 100 on day 4
- Consulted orth for septic arthritis : not likely



- Still swinging fever while on IV Augmentin
  - While cardiac being consulted for rheumatic fever, blood culture came back +ve for MRSA [PVL +ve]
  - Switched Augmentin to Vancomycin 400mg (18mg/kg) IV q6h
  - Arranged urgent US and MRI knee
- 
- US: inflammatory changes of knee joint
  - MRI: osteomyelitis at distal femur with intra-osseous abscess; mild knee joint effusion
  - Consulted surgery

Hosp No: [REDACTED]  
DOB: [REDACTED]  
Sex/Age: F/7Y  
Unit: PYN/PAED  
Ref.:

Location: PYN/PAED/B6G  
Bed: 49  
Doctor Request: [REDACTED]  
Request Loc.: PYN/--/B6G

Date Collected: 21/06/13  
Date Arrived: 21/06/13  
Clinical Details: uri  
Specimen:- Blood (Culture)

Gram stain :-  
Gram positive cocci seen

Blood Culture :-

Organism 1 : Methicillin Resistant Staphylococcus aureus

|              | ORGANISM |
|--------------|----------|
| ANTIBIOTICS  | 1        |
| -----        |          |
| FUSIDIC ACID | S        |
| GENTAMICIN   | S        |
| METHICILLIN  | R        |
| VANCOMYCIN   | S        |

S: Susceptible      M: Intermediate      R: Resistant      +: Positive      -: Negative

Methicillin-resistant staphylococci are resistant to all currently available b-lactam antibiotics. Routine testing of other penicillins, b-lactam/ b-lactamase inhibitor combinations, cepham and carbapenems are not advised.

MSSA / MRSA - "Invasive infections caused by *S. aureus* should normally be treated with iv antibiotics to which the isolate is sensitive e.g. adult dosage of cloxacillin 2g iv q4-6h for methicillin-sensitive strains and vancomycin (in appropriate dosage) for methicillin-resistant strains. Duration of treatment for uncomplicated infections should be no less than 14 days. In case of persistent bacteremia and / or fever, further investigations to exclude deep seated focus of infection, vascular catheter-related infections, and endovascular infections should be considered."

Comment :-

Panton-Valentine Leukocidin (PVL) Gene PCR: Positive

Report date & time: 12:15 on 04/07/13  
Report Destination: RH/--/\*TICN - RH Infection Control Nurse

Print on 04/07/13 12:15

Page No.: 1/2 MR2031/PY





Date Collected: 27/06/13  
Date Arrived: 27/06/13  
Specimen:- Pus  
Site:- (R) FEMUR ABSCESS

Gram stain :-  
WBC: +

Culture :-

Organism 1 : Methicillin Resistant Staphylococcus aureus (Scanty)

| ANTIBIOTICS  | ORGANISM |
|--------------|----------|
| -----        | 1        |
| CLINDAMYCIN  | R        |
| ERYTHROMYCIN | R        |
| FUSIDIC ACID | S        |
| GENTAMICIN   | S        |
| METHICILLIN  | R        |
| VANCOMYCIN   | S        |

S: Susceptible      M: Intermediate      R: Resistant      +: Positive      -: Negative

Comment :-

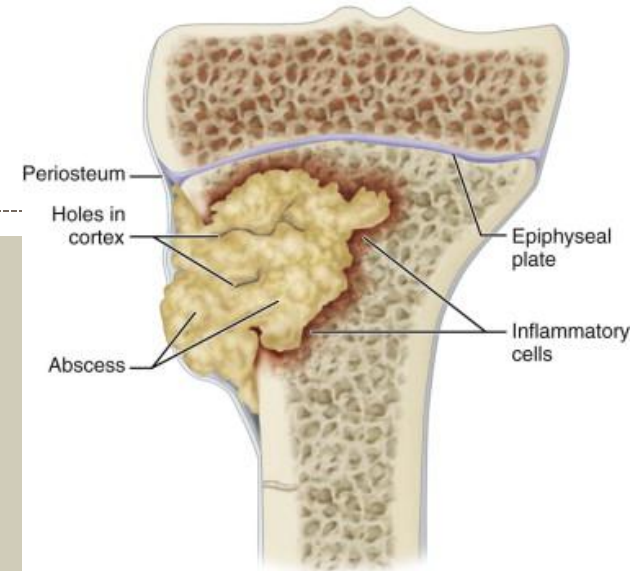
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# Osteomyelitis



- Inflammation of bone
- Incidence ~ 1:5000
- Associated with trauma, surgery
- Immune deficiency, diabetic foot ulcer
- Complement C3, C4 normal
- HIV antibody -ve
- Most commonly affect long bones
- Bacteria are the most common pathogens
- Staph aureus: CA-MRSA > 50%
- PVL +ve MRSA : a virulence factor / marker for complicated infection
- ESR elevated in up to 90% of cases
- Complications: large area of bone necrosis



# Vancomycin therapy



- Pre 4th dose vancomycin level = 10.14mcg/ml
- ID consult: vancomycin for 6 weeks
- Target for osteomyelitis usually between 15-20
- Increased dose to 500mg q6h still only yield a level of 10.56mcg/ml
- Eventually increased to 600mg then 720mg [33mg/kg] q6h = daily dose of >130mg/kg !



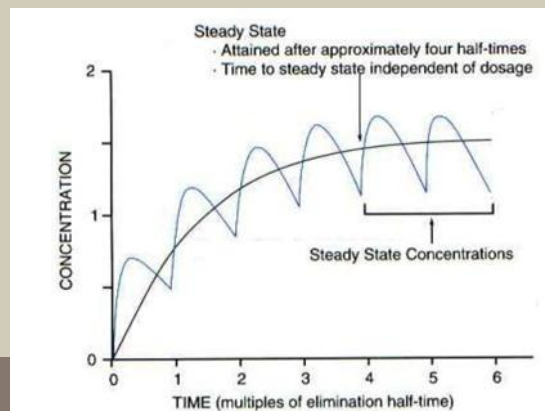
# Vancomycin



- Vancomycin is renally eliminated
- Time-dependent killing
- Trough is important
- Vd usually 0.7 L/kg and not greatly affected by larger amount of body water in paed
- Elimination highly depend on renal function
- At about 3 mths of age, vancomycin clearance doubled that of full term babies
- Continue to increase through 4-8 yrs, when clearance exceed 130ml/min while Vd remains ~ 0.7L/kg
- T<sub>1/2</sub> can be as little as 2-3 hrs
  - L Baurer, Clinical Pharmacokinetic Handbook 2006 105-120



- Fast elimination commonly seen in child 3 – 10 yrs
- Estimated  $T_{1/2}$  for this patient is  $\sim 3.8$  hrs
- At daily dose of 130mg/kg/day, already more than doubled that of usual recommended dose of 60mg/kg/d
- Peak level likely approach toxic concentration range of 50-80mcg/ml [risk of ototoxicity]



# Treatment Options

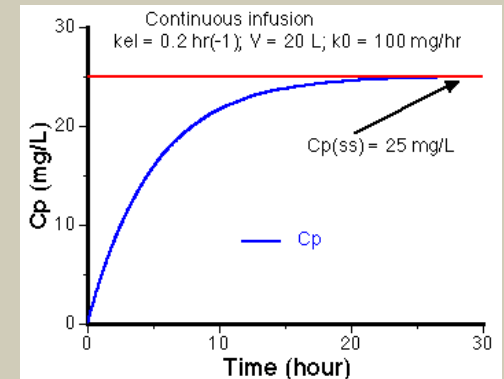


- Increase to q4h dosing?
- Not recommended as dosing interval approaches  $t_{1/2}$ , trough may dramatically shoot up
- Clindamycin: good bone penetration but femur abscess culture showed MRSA resistant to clindamycin
- 2<sup>nd</sup> line treatment: linezolid: expensive, no extensive evidence for treating paed bone infection
- Daptomycin as 3<sup>rd</sup> line

# Pharmacist suggests:



- Vancomycin continuous infusion
- Some published studies in neonates and paediatric patients
- Proven safety
- Maximize the time-dependent activity
- Maintain steady-state levels above MIC
- Require a dedicated line for infusion
- Dosage range 50-60mg/kg over 24hrs, 40-45mg/kg for adolescents\*
- Monitor blood level, urine output, renal function



\*Am J Health-Syst Pharm (69) 2066-2071



- Patient admitted to PICU for PICC line insertion
- Vancomycin is infused through central line
- Previous dose 130mg/kg/d
- MO even wanted range to be 15 – 25 mcg/ml [as in neonatal osteomyelitis]
- Round up to 1.5 g of vancomycin in 500ml D5 [69mg/kg/24 hr] infuse at 22ml/hr started 6 hrs after 720mg dose
- Incompatible with heparin -> none added
- Blood level to be taken 24-36 hrs after start of infusion for steady state [4 – 5 half-lives]
- Blood sample should be taken in peripheral line on the opposite side from central line



- 1<sup>st</sup> level returned 12 hrs after infusion = 28.58 mcg/ml
- [early level + residual drug from last dose]
- Rate of infusion (mg/min) = target conc (mg/L) x drug clearance (L/min)
  - $Cl = 0.695(CrCl) + 0.05$
  - $Rate = C_{ss} * Cl$
  - For  $C_{ss}$  of 20 mcg/ml, rate = 54 mg/hr = 1.3 g per day
- Dose was adjusted to 1.3 g over 24 hrs [ $\sim 60$ mg/kg],
  - Rechecked level 23.7, no change in dosage
- Subsequent levels were obtained every 5 to 7 days = 20.81, 21.47





- CRP , ESR started to drop [ $>100 \rightarrow 12.8, 18$ ]
- Renal function remained stable throughout the 4 weeks vancomycin therapy
- IV site : no signs of phlebitis or infusion reactions
- Usual parameters: elevated SCr 50% over baseline x 2 consecutive days, U/O  $< 1$  ml/kg/hr
- Patient SCr within  $\pm 5\%$ , urine output  $> 3$ ml/kg/hr, no oliguria



Hosp No: [REDACTED] Location: PYN/PAED/A6G  
DOB: [REDACTED] Bed: 12  
Sex/Age: F/7Y Doctor Request: [REDACTED]  
Unit: PYN/PAED Request Loc.: PYN/--/A6G  
Ref.:

Clinical Details: MRSA osteomyelitis

|                |          |          |          |          |          |           |       |
|----------------|----------|----------|----------|----------|----------|-----------|-------|
| Collect Date : | 18/07/13 | 22/07/13 | 02/08/13 | 08/08/13 | 12/08/13 |           |       |
| Collect Time : | 11:20    | 11:47    | 11:28    | 12:57    | 11:41    |           |       |
| Arrive Date :  | 18/07/13 | 22/07/13 | 02/08/13 | 08/08/13 | 12/08/13 |           |       |
| Arrive Time :  | 11:58    | 13:07    | 12:16    | 14:25    | 12:05    |           |       |
| Request No. :  | C5442193 | C5449839 | C5476362 | C5490741 | C5497651 | Reference |       |
| Urgency :      | URGENT   | URGENT   | URGENT   | URGENT   | URGENT   | Range     | Units |

Specimen Type: Blood

|                   |           |           |           |           |           |                  |               |
|-------------------|-----------|-----------|-----------|-----------|-----------|------------------|---------------|
| Sodium            | 137       | 133 *     | 136       | 139       | 137       | 136 - 145        | mmol/L        |
| Potassium         | 4.2       | 4.7       | 4.0       | 3.7       | 4.0       | 3.6 - 5.2        | mmol/L        |
| Urea              | 4.3       | 3.9       | 4.1       | 3.3       | 4.3       | 2.7 - 7.2        | mmol/L        |
| <b>Creatinine</b> | <b>50</b> | <b>51</b> | <b>51</b> | <b>48</b> | <b>49</b> | <b>46 - 61</b> ‡ | <b>umol/L</b> |
| Total Protein     | --        | 85 *      | 78        | 77        | 74        | 64 - 83          | g/L           |
| Albumin           | --        | 45        | 44        | 42        | 44        | 35 - 50          | g/L           |
| Globulin          | --        | 40        | 34        | 34        | 31        |                  | g/L           |
| Total Bilirubin   | --        | 8 *       | 11 *      | 4         | 7         | 1 - 7‡           | umol/L        |
| ALP               | --        | 210       | 227       | 255       | 259       | 156 - 369‡       | IU/L          |
| ALT               | --        | 16        | 12        | 10        | 9         | < 49             | IU/L          |
| Calcium           | --        | --        | 2.48      | --        | --        | See Below‡       | mmol/L        |
| Phosphate         | --        | --        | 1.54      | --        | --        | See Below‡       | mmol/L        |

Comment:

13C5490741 ALP Result verified.

Footnotes:

- Calcium - Reference Range : 2.29 - 2.63
- Phosphate - Reference Range : 1.33 - 1.92
- ‡ - Sex/Age related range given



- On day 26 of vancomycin therapy, PICC line blocked
- Switched to po linezolid and continued for 2 more weeks
- Allow home leave

# Conclusion



- Paediatric patients demonstrated unique pharmacokinetic vs adult
- Vancomycin can be a difficult drug to use in this population
- Continuous infusion offers a safe and inexpensive alternative
- Easy to titrate to desire level
- Cost comparison [per day]:
  - Vancomycin: \$40.5
  - Linezolid: \$423 [po] ; \$1335 [IV]
- Challenges: blood sampling, presence of a dedicated line / central line, culture +vs cases



- **Pharmacist role:**

- Therapeutic Drug Monitoring
- Monitor trough [aminoglycoside, vancomycin]
- Peak and trough [e.g. endocarditis]
- “peak” to calculate actual kinetics
  - ✦ Vancomycin level too high, withhold dose to recheck level ->  $C_{max}$  and  $C_{min}$  available

Thank you

