New technologies to support dose optimisation

29th European Congress of Clinical Microbiology and Infectious Diseases
ECCMID 2019

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New technologies to support dose optimisation: where will we be in 2024?

Declaration

• No conflicts to declare
Future technology for dose optimisation

- Current challenges
- Biosensor technology
- Future wearable technologies
- Linked PK-PD monitoring
- Integrated individualised dosing systems
Antibiotic PK-PD

Pharmacokinetics (PK)
Drug concentration vs. time

Pharmacodynamics (PD)
Drug effect vs. concentration

PK-PD
Dose - effect relationship

Dose
Clinical response

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Dosing is a dynamic process

Inter-individual variability

Race
Weight
Age
Gender
Medications
Comorbidities

Intra-individual variability

Circulatory changes
Organ support
Renal failure
Clearance
Fluid balance
Hepatic dysfunction

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Why explore individualised antibiotic dosing?

- Improve treatment outcomes
- Prevent toxicity
- Minimize the impact on antimicrobial resistance
- Utilisation of resources
- Enhance our understanding of individual PK-PD
Current approaches to individualise therapy

Current examples
Therapeutic drug monitoring
Dose optimization software
Prolonged infusions
New PD indicators
To deliver truly individualised therapy

Ideally....

Real-time pharmacokinetics

In-vivo pharmacodynamic indices
- Organism
- Host

Individualised, automated methods for dose adjustment
Barriers to wider implementation of TDM

**Risk of exposure to HCW’s**
- Laboratory
- Checked in
- Spun
- Analysed
- Interpreted
- Reviewed by prescriber
- Reported

**Valid assay**
- Equipment / staff costs
- Delays in reporting

**Stability of drug**
- Timing samples

**Population level estimates**
- Expertise to interpret

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Rawson, O’Hare et al, JAC; 2018

ESCMID eLibrary by author
Electrochemical Biosensors

**Potential benefits**
- Miniaturised
- Portable
- Easy to use
- Point-of-care
- No HPLC required
Biosensors in infection management

- Bugs
- Drugs
- Sensors
- Biomarkers
- Patient

Real-time measurement of small molecules directly in awake, ambulatory animals

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Wearable technology for dose optimisation
MISBLA study – Penicillin monitoring

Recruitment & preparation

- 10 Healthy Volunteers
- Pen V 500mg QDS Steady state

Study day

- Sensor worn for 6 hours
- Tissue microdialysis
- Rich PK analysis

Outcomes and analysis

- Calibration of microneedles
- Proof-of-concept

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In-vivo penicillin monitoring

Microneedle raw data output
In-vivo penicillin monitoring

Microneedle calibrated to concentration
In-vivo penicillin monitoring
A role for microneedle technology

Benefits

• Direct in-vivo monitoring
• No need for HPLC / internal standard
• Application to wide range of settings
• Multiple agent sensing
• Potential to optimise multiple compartments

Ongoing challenges

• PK variation in critical illness
• Presence of inhibitors
• Paucity of data for agents
• Paucity of data for biomarker sensing
Is real-time measurement of in-vivo PD indices possible?

C-Reactive Protein

- Acute Phase Response protein
- Kinetics well understood
- Rationale for predicting response to infection
- ISF Indistinguishable in terms of protein diversity compared with plasma
- Over 60 types of CRP sensor reported
Predicting antibiotic PD using CRP

\[
\frac{dX(1)}{dt} = R(1) + X(2) \cdot Kpc - X(1) \cdot \left( \frac{SCL}{V} \right) - X(1) \cdot Kcp
\]

\[
\frac{dX(2)}{dt} = X(1) \cdot Kcp - X(2) \cdot Kpc
\]

**C-reactive protein**

\[
\frac{dX(3)}{dt} = \left( KCRP \cdot X(3) \cdot \left[ 1 - \frac{X(3)}{POP_{max}} \right] \right) - \left( KCRP \cdot X(3) \cdot \left[ \frac{X(1)}{V} \right]^{n} \right) - \left( \frac{EC_{50}^{n} \cdot X(1)}{EC_{50}^{n} \cdot X(1)^{n}} \right)
\]

**Antibiotic PK**

**Individual AUC:EC_{50}**

**Antibiotic PD**

**Antibiotic**

- **Teicoplanin**
  - Paediatrics
- **Vancomycin**
  - Adults

Ramos-Martin, et al. JAC; 2016, Rawson, Charani et al, TDM; 2018

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Evidence for in-vivo biomarker monitoring

Lactate important marker for sepsis

Ex-vivo validation on plasma

In-vivo monitoring with exercise bike challenge

Proof-of-concept
Next steps

- Closed-loop control of penicillin delivery in healthy volunteers
- Antibiotic / biomarker sensing in patients
- Validation of new PK-PD indices
Where will we be in 2024?

• Microneedle based technology offers new frontier in individualised antimicrobial therapy

• New array of wearable technologies to support in-vivo PK-PD evaluation

• Greater understanding of antimicrobial PK-PD

• Automated dose optimisation
Acknowledgements