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L0032 Real-time, minimally invasive penicillin monitoring: a first-in-human evaluation of microneedle-based biosensor technology

Timothy Rawson*[1], Sally Gowers[2], David Me Freeman[2], Richard Wilson[1], Sanjiv Sharma[3], Mark Gilchrist[4], Alasdair P. Macgowan[5], Andrew Lovering[6], Pantelis Georgiou[2], Tony Cass[2], Danny O'Hare[2], Alison H. Holmes[1]

[1] Hammersmith Hospital, Imperial College London, London, United Kingdom, [2] Imperial College London, London, United Kingdom, [3] Swansea University, Sketty, United Kingdom, [4] Imperial College Healthcare NHS Trust, London, United Kingdom, [5] University of Bristol, Bristol, United Kingdom, [6] Southmead Hospital, Bristol, United Kingdom

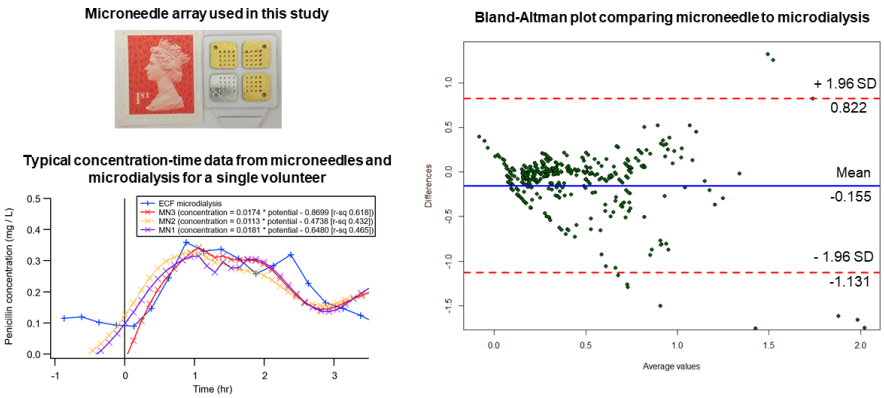
Background: The demonstration of wide pharmacokinetic variation between individuals has led to calls for enhanced methods of drug monitoring to facilitate truly individualised antimicrobial dosing. We report the first-in-human evaluation of real-time penicillin monitoring using a minimally invasive microneedle-based penicillin biosensor.

Materials/methods: Ten healthy participants were recruited at Imperial College London, Clinical Research Facility (CRF). Participants took five doses of oral phenoxymethylpenicillin (500mg, 6 hourly) prior to attending the CRF. For the sixth penicillin dose, individuals had venous blood (via cannula, T=-30,0,10,20,30,45,60,90,120,150,180,210,240 mins) and interstitial fluid (via microdialysis, every 15 mins) sampled. Individual free blood drug levels were estimated. Volunteers wore three microneedle penicillin biosensors during this period to provide real-time monitoring of interstitial fluid penicillin. Volunteers completed visual analogue scales to explore tolerability of wearing microneedle biosensors (0 = no discomfort, 10 = significant pain). Penicillin concentration data obtained from the microneedles was filtered using locally-weighted-scatter-plot-smoothing (LOESS) and compared to free blood and microdialysis (gold standard) penicillin pharmacokinetics using non-compartmental analysis. Area-under-the-curve (AUC) was compared. Bias and limits of agreement were investigated with Bland-Altman plots. The limit of detection for the microneedle biosensors was estimated.

Results: Mean (SD) participant age was 42 (14) years. Severn (70%) were male. Mean (SD) length of time monitored from dose six (T=0) was 224 (28) minutes. Mean (SD) AUC was 1.56 (0.29) mg*h/L for free blood, 1.56 (0.85) mg*h/L for microdialysis, and 1.60 (1.04) mg*h/L for microneedle curves. *Figure 1* demonstrates a typical comparison of microneedle and microdialysis penicillin monitoring for one individual and Bland-Altman assessment of data from all 30 microneedle biosensors compared to microdialysis. In total, 440 time points were compared with mean (95%CI) difference between measurements -0.15mg/L (95%CI: 0.20 - -0.11). Limit of detection for the microneedles was estimated at 0.10mg/L. The microneedle was well tolerated by participants with mean (SD) pain score 0.4 (0.8) cm compared to microdialysis insertion that scored 1.9 (3.8) cm.

Conclusions: This study demonstrates proof-of-concept for real-time, microneedle-based, sensing of antimicrobials in humans. Future work will now look at incorporating closed-loop control functions to facilitate automated drug delivery.

Figure 1. Example of microneedle and microdialysis data for individuals and grouped analysis of all 30 biosenors using a Bland-Altman plot



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