Comment

β-lactam microneedle array biosensors: a new technology on the horizon

In The Lancet Digital Health, Timothy Rawson and colleagues’ report a proof-of-concept study evaluating real-time drug monitoring of penicillin in the extracellular fluid (ECF) of ten healthy volunteers during 6 h, using a microneedle biosensor applied to the forearm. Microneedle biosensor measurements of the ECF penicillin concentration showed comparable results to the standard techniques used to measure drug concentrations (microdialysis and serum concentration measurement in blood samples). Furthermore, the microneedle biosensor allowed for a real-time continuous measurement of penicillin concentration in the ECF. Rawson and colleagues concluded that further evaluation of the biosensor in specific patient populations was necessary to further validate these results in actual clinical scenarios. The microneedle biosensor might further be the mainstay of a closed-loop system for automated drug delivery—ie, allowing for continuous measurements of antibiotic concentrations and automated adjustment of antibiotic infusion according to these measurements.

An improved understanding of antimicrobial pharmacokinetics (PK) in critically ill patients has rendered the decade-old dogma one-size-fits-all untenable. The multitude of pathophysiological changes and the large interindividual and intraindividual differences in PK call for individually calculated doses of antibiotics rather than a fixed dosing regimen for all patients and is referred to as customised drug dosing. The core of this approach is to account for the specific pharmacokinetic-pharmacodynamic (PK/PD) profile of antibiotics. PK/PD links dose with an endpoint of interest. Usually that endpoint of interest involves patient mortality or survival, clinical cure, bacterial killing, or the emergence of antimicrobial resistance. This understanding of PK/PD becomes very important to make sure that we are choosing individual doses that are more likely to achieve the chosen endpoint. Besides individual doses, customised drug dosing also includes extended dosing regimen, such as the prolonged or continuous infusion of, for example, β-lactams or vancomycin. The aim of customised drug dosing is to ensure optimal exposure to a defined antibiotic serum concentration to maximise treatment success. Mainstays of customised dosing are therapeutic drug monitoring and PK-dose simulations that include, for example, renal function and the use of renal replacement therapy.

Therapeutic drug monitoring is not ubiquitously available because of high costs and the need for trained pharmacists, among other factors, and determination of serum concentrations is not standardised. Another problem is the translation of therapeutic drug monitoring results into actual changes of dose in the intensive-care unit. Rawson and colleagues show that it might be possible to easily and reliably measure real-time penicillin concentrations in the ECF using a small and easy to wear microneedle biosensor. The results of measured serum concentrations and the results of the microneedle biosensor are comparable, and open the field to a new and easy tool to measure serum concentrations, possibly making therapeutic drug monitoring-guided dosing for the individual patient available to a broader range of health-care providers. Moreover, Rawson and colleagues propose the use of a microneedle biosensor as part of a closed-loop system for the administration of β-lactams. Although being far from clinical implementation, targeted and automated application of antimicrobials to achieve and maintain a specific PK-target is of utmost importance, when powerful antimicrobials are still used unjudiciously and antimicrobial resistance rates are ever rising.

It will be interesting to see how the microneedle biosensor will perform in a population of patients with infections and, especially, in critically ill patients in the intensive-care unit, where real-time measurement of concentrations would be of importance. The present study measured penicillin (a substance that would rarely be used alone in critically ill patients) concentrations in the ECF. Therefore, another often debated question is if microneedle biosensors can be implanted to measure not only in the ECF of the dermis but also at the site of infection. Measuring β-lactams at the site of infection rather than in blood or dermal ECF would aid clinicians in determining the effectiveness of the antimicrobial therapy. Except from the closed-loop application and automated dosing, more data are needed to answer the question why a continuous measurement of drug concentrations is not standardised. Another
concentration is helpful and superior to the regular therapeutic drug monitoring. Leaving aside the closed-loop system of automated drug delivery, therapeutic drug monitoring from blood samples can easily be done (intravenous and arterial lines are usually used in intensive-care units) and, from a clinical point of view, appears sufficient in answering the important questions (eg, determining serum concentrations and adaption of dose). Whether real-time measurement might accelerate and improve dosing remains to be evaluated. However, the microneedle biosensor might be of help in paediatric and neonatal intensive care, where intensivists try to restrict blood samples to a minimum.

We also look forward to seeing how the microneedle biosensor performs with other β-lactams and if, in the future, other clinically important substances with a narrow therapeutic window or potentially toxic effects (vancomycin) could be measured as well. Data of continuous infusion of piperacillin or tazobactam imply that overdosing might be of importance in critically ill patients. In that sense, we were eager to know if the microneedle biosensor could also be used to reliably detect potentially harmful β-lactam concentrations and act as a monitor for toxicity.

Rawson and colleagues show that the microneedle biosensor-technology is generally able to measure penicillin concentrations in the ECF with an accuracy comparable to that of microdialysis and measurements from patient serum. However, the present study is a proof-of-concept. Further investigation will show if this technology will find its way into clinical practice and we anticipate that this tool has the potential to change the way we do antimicrobial treatment.

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We declare no competing interests.

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