


Detective work on drug dosage

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Therapeutics

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Patients differ in their requirement for, and response to, various drug doses. A general platform that allows continuous monitoring of drug levels in the blood of rats may open the door to patient-specific dosing.

Choosing the right drug dose for a particular patient is more of an art than a science. For example, the dosage of most drugs is simply based on patients' age: “Adults and children 12 years and over, take 2 tablespoons every 6 hours,” for example. In reality, there is patient-to-patient variability in drug metabolism and excretion, highlighting the need for accurate and patient-specific approaches to monitor drug concentration after administration. Taking a big step towards this goal, Ferguson *et al.*¹ describe, in a paper published in *Science Translational Medicine*, a detection system that allows real-time tracking of drugs in the blood.

For a few relatively toxic drugs, several factors, including gender, body mass or body surface area, are taken into account to better estimate the effective dose. For drugs with a particularly narrow window between the minimum effective and toxic doses, clinicians often opt for 'peaks and troughs' measurements. In this approach, blood is drawn half an hour after a drug dose is given, when the drug's concentration in the blood is likely to be highest; a second sample is then drawn immediately before the next dose is due. From these two isolated data points the drug's pharmacokinetics (the rate at which its concentration in the blood falls) is inferred, and from that the optimal dosing regimen for that specific patient is determined.

Even the most advanced methods used to estimate an appropriate drug dose are rather crude and imprecise. Existing measurements of pharmacokinetics typically involve drawing blood and sending it to a central lab for analysis. The ability to monitor drug levels in the blood continuously in real time in the clinic would vastly improve the precision of such measurements. This, in turn, would greatly improve the ability to tailor drug dosing to a patient's specific needs.

Measuring drug levels continuously requires a technology that is reversible, so that the sensor's response rises and falls in concert with fluctuating drug concentrations. Moreover, the technology must be continuous, of course, and so should not rely on wash steps or other batch processes. Finally, it must be sufficiently selective to be used on whole blood. Unfortunately, although conventional analytical methods, including chromatography, spectroscopy and immunochemistry, often have one or more of these attributes, no general approach has achieved all these goals simultaneously. There are ways to measure a few specific molecules in the body in real time (for instance, blood glucose levels in patients with diabetes), but these are single-analyte sensors that are not easily generalizable to the detection of other molecules.

Ferguson *et al.* describe a sensor that cleverly links the above three technologies; they call it microfluidic electrochemical detector for *in vivo* continuous monitoring (MEDIC).

The sensing technology underlying this platform is a reagent-free electrochemical device^{2,3} that uses the binding-induced folding of aptamers⁴ (artificially selected nucleic acids that bind specific molecular targets) to signal the presence of a given analyte. This reagent-free, wash-free, sensing architecture has previously been shown⁵ by some of the same authors to support continuous measurements in flowing, undiluted blood serum. The approach fails, however, when the sensor is challenged with whole blood, owing to the nonspecific adsorption of molecules onto the electrode surface, which progressively deactivates the associated aptamers — thereby leading to baseline drift in the output signal.

To eliminate this drift, Ferguson and colleagues took a two-pronged approach. The first was to place the sensors in a microfluidic device that insulates them with a micrometres-thick stream of buffer. Blood continuously collected from the subject (by a cannula) is drawn into the device, where it forms a laminar flow over this buffer (Fig. 1). Because the drug molecules are small, they quickly diffuse through the buffer layer to reach the sensor surface. The much larger blood cells and other large interfering agents diffuse too slowly to reach the buffer stream, so sensor fouling is essentially eliminated.

Figure 1: MEDIC in action.

Ferguson *et al.*¹ describe a detector they call MEDIC, which could potentially be used as follows. A patient's blood enters the multilayered device, where it flows along a microfluidic channel and encounters, but does not mix with, a separate stream of saline buffer. The buffer layer acts as a continuous flow filter: small-molecule drugs rapidly diffuse to the surface, whereas more slowly diffusing large proteins and blood cells cannot reach it. Aptamer probes, which are immobilized on multiple electrodes along the top of

the channel, act as molecular switches: on binding to a specific drug, they change shape and induce an electrical current. The current is directly related to the concentration of the target drug, allowing accurate quantification. (Figure adapted from ref. 1.)

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The authors' second advance was to interrogate their electrochemical aptamer probes using a method, known as square-wave voltammetry, operating at two discrete frequencies. Specifically, they identified matched frequency pairs at which the output signal drifts in concert while responding very differently to the presence of the target. Taking the difference between these two signals effectively eliminates drift. Combining the two approaches, the authors' device achieves multi-hour, continuous measurements on whole, undiluted blood with baseline stabilities in the submicromolar range of drug concentration.

The team demonstrated the ability of the MEDIC platform to monitor the chemotherapeutic drug doxorubicin and the antibiotic kanamycin in the blood of anaesthetized rats over the course of several hours. The pharmacokinetics derived correspond to long-established values⁶ obtained by laboriously drawing blood samples and then, much later, measuring each by using chromatography. In the present paper, by contrast, the measurements were made in real time, which not only is convenient but also improves their precision.

There are some disadvantages to this platform, however. MEDIC requires continuous blood draws (of just a few hundred microlitres per hour) and a pump to maintain the flow of buffer through the device. It is therefore unsuitable for continuous, real-time monitoring of metabolites or drugs in the blood of a mobile patient going about their daily life. Nevertheless, by enabling convenient, high-precision measurements of pharmacokinetics in the clinic, the technology could fuel further advances in personalized medicine by supporting truly individualized dosing regimens. Indeed, the ability to monitor blood drug concentrations in real time could pave the way to proactive, high-precision dosing in which drug delivery is modulated on the go in response to hour-to-hour changes in a patient's metabolism or health status. Such feedback-controlled drug delivery could, in turn, open the door to therapies in which drugs with previously unduly complex dosing regimens or unacceptably narrow therapeutic indices are administered safely and effectively.

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