Breaking the Therapeutic Drug Monitoring Logistics Barrier

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Therapeutic drug monitoring (TDM) is one of the most complex laboratory testing processes in modern laboratory medicine practice. Based on the simple engineering principle of feedback control, TDM strives to regulate an individual’s exposure to a drug by measuring the drug’s concentrations, usually at steady state and at distributional equilibrium, and then use these concentrations to determine the drug’s new dose. Unlike a thermostat in a home that can measure temperature in real time and trigger the introduction of more heat from a furnace until a target temperature is reached, drug concentration monitoring currently requires multiple steps, including administration of a drug at the correct dose, collection of one or more blood samples at precise times following drug administration, transport of these samples to a laboratory where they can be analyzed, and then returning the concentration results to a physician, who can adjust the future dose. Moreover, the exposure to a drug is often estimated through fitting of sparsely sampled concentration data to pharmacokinetic models that are sometimes complex. In some cases, only a single trough concentration can be practically collected due to the busy nature of many outpatient clinics. Successful TDM, therefore, requires that a team comprising a physician, pharmacist, nurse, phlebotomist, and laboratory professional all work closely together to coordinate and perform this complex monitoring process correctly. Each step in this complex process affords the possibility of error, and error is always inevitable. Controlling error in the total testing process is tantamount to TDM success.

Laboratory accreditation and proficiency testing programs, along with innovations in laboratory technology, have done a remarkable job of improving the quality of clinical laboratory testing. The analytical error (combined imprecision and bias) for TDM tests is often well below 10% for most measured drugs. Drug manufacturers and pharmacists also apply rigorous QC and quality assurance principles to assure that an accurate dose of a medication is provided to patients. In between the administration of a drug and analysis of its concentration in the laboratory exists a proverbial “TDM black box,” in which the timing of blood collection in relationship to drug administration is often subject to great uncertainty. This is due in no small part to the complicated logistics of coordinating dosing with sample collection in the busy clinical setting. For many drugs, this uncertainty can render the whole TDM process useless and perhaps even dangerous, representing the greatest challenge to successful application of TDM.

The recent study reported by Ferguson et al. in *Science Translational Medicine* represents a possible way to crack open the TDM black box and perhaps make TDM far more clinically useful. These investigators describe a Lab-on-a-Chip device termed microfluidic electrochemical detection for in vivo continuous monitoring (MEDIC). This device combines a novel microfluidics system with a DNA aptamer-based electrochemical biosensor to continuously measure small molecules. Taking advantage of the changes in secondary structure of a DNA aptamer upon binding to a small molecule like a drug, Ferguson et al. show the ability of gold-immobilized aptamers to transduce an electrochemical signal in proportion to the concentration of the aptamer-binding drug in whole blood. Most impressively, they demonstrate the feasibility of applying this technology to the real-time in vivo monitoring of the distributional pharmacokinetics of the free concentrations of 2 drugs, doxorubicin and kanamycin, in rats over the course of 4 h.

DNA aptamers are one of the key components of the MEDIC device. Aptamer technology, which has been around for close to 2 decades, provides a platform for generating nucleic acid polymers capable of specific and high-affinity binding to a wide range of molecules. Serving as an alternative to antibodies, aptamer technology has a particularly attractive feature, the ability to readily generate specific RNA or DNA aptamers through the screening of a randomly generated oligonucleotide library (often termed selective evolution of ligands by exponential enrichment, or SELEX) over the
The MEDIC device provides a highly innovative approach to bringing the analytical laboratory to the patient’s bedside. The possibilities are enormous, but so are the challenges. What makes the MEDIC technology unique is the ability to make almost continuous TDM measurements using microliter quantities of whole blood. The miniaturization of the drug sensor is made possible by the electrochemical sensor. In addition to the inexpensive and analytically sensitive nature of electrochemical detection, the ability to fabricate small electrochemical devices is one of the main benefits of this technology over spectroscopic or chromatographic methods that form the mainstay in the modern clinical laboratory. The other major hurdle that Ferguson et al. had to solve was the interference created by cellular and protein components in whole blood that deposit on a biosensor and thereby reduce responsiveness, a process that has been termed fouling. Fouling represents a major challenge, especially for implantable biosensors that require continuous operation over time. To solve this problem, Ferguson et al. took advantage of a unique fluid-based barrier approach based on laminar flow of an isotonic buffer over the sensor to shield it from these interferents, which they termed a continuous diffusion barrier. At least within the timeframe of the 4-h monitoring reported, the authors demonstrate minimal loss of sensor responsiveness. One of the next logical steps appropriate for the TDM application of this technology will be to assess its performance in human study participants, as the authors performance in human study participants, as the authors

course of days to weeks (5). The chemistry of nucleic acids is also well developed, permitting the simple and cheap introduction of modifications such as the methylene blue redox reporter and free thiol required for coupling of the aptamer probe to the microfabricated gold substrate necessary to generate an aptamer-based electrochemical sensor.

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Implantable, continuous biosensors are already in use for continuous glucose monitoring in patients with diabetes. Many of the commercially available glucose-monitoring devices, like MEDIC, utilize electrochemical sensors for the continuous measurements of whole blood. It is therefore conceivable that MEDIC or a similar device could be applied to the tenacious problem of TDM. Like continuous glucose monitoring, periodic measurement of a drug by a reference method would be required for recalibration of a device like MEDIC. Given that current clinical monitoring of therapeutic drugs sometimes requires 7 or more samples to determine the pharmacokinetic behavior of a drug in an individual (e.g., busulfan monitoring in bone marrow transplantation), a few calibration measurements that could be collected at random instead of the current strict timing required for current TDM would be a welcome change. Unlike the continuous monitoring of glucose, for which devices require frequent replacement, monitoring of therapeutic drugs does not need to be a long-term endeavor. In most cases, monitoring for 6-12 h or less may be quite sufficient to characterize the pharmacokinetic behavior of a drug in an individual patient.

The costs associated with drug therapy failure and adverse effects can be immense. Personalized diagnostics like TDM can reduce both. A simple technology like MEDIC could allow us to overcome many of the challenges associated with implementing complex TDM procedures, which currently impede TDM use in busy clinics. It is impossible to know the future of this type of technology. Nevertheless, the MEDIC device described by Ferguson et al. in their proof-of-concept study gets us a great deal closer to reaching “TDM nirvana.”

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References