Letter to the Editor

Comparison of vancomycin concentrations in blood and interstitial fluid: a possible model for less invasive therapeutic drug monitoring

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Using just a drop of blood, many hundreds of drugs and physiological metabolites can be analyzed at great speed and with remarkable accuracy. The techniques used for these analyses in laboratory medicine include, among many others, spectrophotometric assays, immunoassays and liquid chromatography coupled with mass spectrometry. However, the starting point for each of these methods is still the drawing of a blood sample. In many patient populations, obtaining sufficiently large and frequent blood samples for analysis is not a problem. There are, however, groups of patients, such as patients with fragile/"bad" veins, neonates, infants and children, for whom blood sampling, in particular repeated blood sampling, is difficult. As such, efforts are being made to replace frequent blood drawings, for example, in renal patients by optical measurements [e.g., hemoglobin and cytochrome analysis with an infrared probe directly through the skin (1)] and in diabetes patients by enzyme-based measurements [e.g., blood glucose analysis based on the glucose-oxidase enzyme technology (2)]. These methods are minimally invasive, operating with a subcutaneous sensor, sensor-based microdialysis or reverse iontophoresis. Some of these techniques are expected to replace standard capillary blood analyses in a portion of the patient population.

To be able to eliminate the need for blood sampling, we are proposing an alternative drug sampling method for drugs that warrant therapeutic drug monitoring. The technique is based on accessing the interstitial fluid (ISF), which is essentially an aqueous solution of amino acids, sugars, fatty acids, coenzymes, hormones, neurotransmitters, salts, drugs and cellular waste products. ISF has a composition similar to that of blood plasma, since red blood cells, platelets and plasma proteins cannot pass through the walls of the capillaries. A recently introduced method of subcutaneous ISF sampling involves the use of an ultrafiltration device. It consists of three loops of a tubular membrane with a molecular weight cut-off of 30 kDa and an attached tube, which can be connected to sampling vials. The loops can be introduced subcutaneously through a trocar. The ISF and small molecules contained within (below the exclusion molecular weight) will enter through the pores and will then be removed by an applied vacuum from, for example, a blood sampling vial. Unlike the case with microdialysis, no dilution of the ISF will take place (see Figure 1). Subcutaneous ISF sampling has many advantages over blood sampling. On the one hand, it is relatively non-invasive, causes minimal pain, produces no bleeding, lacks complications associated with hemolysis and requires minimal sample clean-up. On the other hand, drug appearance in the ISF could be delayed (2) and the ISF composition may be tissue/location-dependent (3), making consistent sampling (i.e., with respect to tissue location) important.

The objectives of the current pilot study were: 1) to demonstrate the feasibility of sampling and obtaining reliable drug concentration readings in ISF for vancomycin and 2) to ascertain if vancomycin concentrations in ISF and blood are comparable. Vancomycin, a glycopeptide antibiotic, was used as a probe in a rabbit model for two main reasons: 1) it commonly undergoes therapeutic drug monitoring; and 2) it is minimally protein bound and, thus, a good correlation between blood and interstitial fluid concentrations may be expected (4).
Four New Zealand white female rabbits (2.2, 2.4, 3.1 and 3.5 kg) were obtained from Charles River Laboratory (Wilmington, MA, USA), housed in the Animal Care Center at The University of British Columbia, and fed water/food ad libitum on an approved animal protocol. After an adequate acclimatization period, a gas-sterilized ultrafiltration probe (UF-3-12, Bioanalytical Systems Inc, West Lafayette, IN, USA) for ISF collection was implanted between the shoulders under anesthesia. This probe (Figure 1), consisting of three tubular ultrafiltration membranes of 12 cm length that were folded in loops of 6 cm length and had a molecular weight cut-off of 30 kDa, was tunneled under the subcutaneous tissue (approx. 7 cm) and secured with a rabbit “jacket” stockinette. Ultrafiltration (5) is similar to microdialysis in as-far as similar membranes are used and they both access interstitial fluid (6). However, the driving force in ultrafiltration is a vacuum to remove the formed ISF, while microdialysis uses external liquids and diffusion as the driving forces for probe extraction. These different modes of extraction as well as large differences in extraction volume make the ultrafiltration method more susceptible to probe recovery problems, specifically adsorption issues.

On day 3 post-implantation, a non-toxic intravenous bolus of vancomycin HCl (20 mg/kg, Hospira Healthcare Corporation, Montreal, QC, Canada) was administered into the ear vein. Subsequent ISF samples were obtained from the ultrafiltration probe using BD Vacutainers® (Becton Dickinson, Mississauga, ON, Canada). Blood samples were taken from the ear artery through a 22 gauge over-the-needle catheter. Vacutainers® were attached to the ultrafiltration probe and the ISF was collected starting 20 min before the first sample time point. Vacutainers® were then replaced every time a blood sample was taken at 0, 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 and 8 h. ISF and blood concentrations were measured by particle-enhanced turbidimetric inhibition immunoassay in serum (QMS® Vancomycin Immunoassay, Thermo Fisher Scientific, Waltham, MA, USA). In addition, an in vitro experiment was performed with an ultrafiltration probe immersed into a vancomycin solution, to evaluate how much of the drug adsorbs to the membrane surface. Pharmacokinetic (PK) parameters [area under the curve (AUC 0 – 8h), T max (time to maximum concentration), C max (maximum concentration)] were generated using non-compartmental analysis in Phoenix™ WinNonlin® 6.1.

Glucose concentrations, known to equilibrate between ISF and blood (7), served as the positive control and were measured with a Bayer Contour® glucose meter. The rabbits recovered uneventfully and no clinical signs of infection were detected. Glucose concentrations in ISF and blood were superimposable (Figure 2), confirming the suitability of the animal model. The AUC of vancomycin in ISF (98.2±6.4 µg×h/mL, mean±SD) was comparable to blood (86.4±18.7 µg×h/mL), but the C max was much lower (32.1±2.6 vs. 72.1±16.0 µg/mL, ISF vs. blood) and there was a distribution delay (T max of 1.0±0.2 vs. 0.2±0.1 h, ISF vs. blood) (Figure 2). The concentration-time profiles from each rabbit were very similar, resulting in relatively small standard deviations (Figure 2). In the in vitro experiment, elution concentrations at different time points were found to be identical to the initial vancomycin concentration (98.1±2.7%) and drug loss through adsorption onto the ultrafiltration probe thus appears to be negligible.

Figure 1 The ultrafiltration probe is implanted and applied vacuum (e.g., a Vacutainer®) removes ISF containing potentially dissolved drugs and other small molecular weight molecules at 1–2 µL/min. Not to scale.

Figure 2 Concentration-time profiles of glucose and vancomycin in rabbits (mean±SD, n=4).
Our novel finding in rabbits that vancomycin exposure (AUC) in ISF was similar to blood suggests the feasibility of monitoring vancomycin concentrations in ISF. However, there was an apparent measurement delay of about 0.8 h and the $C_{\text{max}}$ was much reduced (Figure 2), which warrant further PK modeling. The measurement delay in ISF has also been reported for glucose (2), although some have argued that the phenomenon may be an artifact of the measurement device (8). As such, further investigations are needed to determine if measurement delays derive from the sampling method. Furthermore, ultrafiltration results should be compared to the more commonly employed microdialysis method in pre-clinical investigations. In patients with post-traumatic hemorrhage, Caricato et al. (3) showed that vancomycin ISF concentrations in the abdominal area agreed with serum concentrations, but the concentration in the cerebral tissue surrounding brain lesions was found to be much lower and also far below effective concentrations. A site-specific ISF composition will have to be included in a future study to further prove the suitability of ISF sampling.

To the best of our knowledge, no other study has directly compared PK parameters of vancomycin in blood and ISF. While an implantable ultrafiltration device is not suitable for clinical trials nor practical for clinical use, our study findings (that vancomycin ISF concentrations are detectable and drug exposure in ISF correlates with blood exposure) provide an impetus for new ISF sampling approaches such as the recently described microsystem (9). These new ISF sampling methods may be applied to numerous drugs, other than vancomycin, for which therapeutic drug monitoring has demonstrated utility (10).

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