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Noninvasive Lithium Monitoring

Iontophoresis, a technique involving the application of a low electric current to the skin, has been used for drug delivery for several decades, and approved iontophoretic drug delivery devices are finally reaching the market. The mechanisms of drug transport are based on electromigration of charged molecules and/or electroosmosis (1).

As iontophoresis is electrically symmetric, endogenous substances are extracted during current application. Consequently, iontophoresis has been recently recognized to be a novel noninvasive method to obtain specimens for measurements of concentrations of endogenous compounds of interest. Because analyte extraction proceeds in the opposite direction to drug delivery, this noninvasive extraction has been termed "reverse iontophoresis". The potential exists to use this technique in clinical chemistry without blood sampling (2). The amount of substances extracted across the skin has been linearly related to the subdermal concentration and, by extrapolation, to the systemic concentration (3).

Noninvasive sampling methodologies, including reverse iontophoresis, are of obvious benefit to all patients: Pain and discomfort are decreased. Risk of infection is reduced. Sampling can be performed more frequently. Ambulatory monitoring is possible provided that a method to analyze the molecule of interest is included in the system. Alternatively, the samples extracted by the device could be sent to a clinical laboratory. Reverse iontophoresis devices can be miniaturized to portable systems that record data for several hours.

Reverse iontophoresis has some limitations. A very sensitive and specific analytical method is required to measure very small amount of the analyte that is extracted. As the skin can accumulate the analyte, reverse iontophoresis could provide information on this local reservoir rather than on blood concentration. Steady-state rates of extraction are not reached instantaneously, requiring an undetermined duration of current application. High protein binding can hinder analyte extraction.

Because a noninvasive tool to monitor glycemia in diabetic patients would be of immense medical benefit, attention has focused first on glucose monitoring (3). Reverse iontophoresis is now exploited for the noninvasive monitoring of glucose. After a warm-up period of 3 h and calibration by a conventional "finger-stick" method, extracted glucose amounts can be correlated to glycemia for 12 h. The miniaturized portable system is reusable, whereas electrodes and reservoir are disposable (4).

In addition to blood chemistry and, in particular, glucose monitoring, applications of reverse iontophoresis that have been envisaged include the detection of diagnostic markers [such as phenylalanine (5) and prostaglandin E₂] and monitoring of therapy with drugs such as valproate, phenytoin, and lithium (6-8).

Most of the studies on noninvasive drug monitoring by

use of reverse iontophoresis have been performed in vitro: the subdermal compartment mimicking the blood contains various concentrations of drug, which is extracted by the current through the skin sample placed in a diffusion cell. Drug concentrations in the anodal compartment for negative drugs or cathodal compartment for neutral or positive drugs are then analyzed. These in vitro studies were important to develop the method and prove the concept that drug extraction by reverse iontophoresis is proportional to blood concentration. This in vitro approach was explored for model drugs (3) and was extended to drugs such as valproate, phenytoin, and lithium, which have low therapeutic indexes (6-8). In vitro studies demonstrated the linearity of Li⁺ extraction from a physiologic buffer that was made to simulate a pharmacokinetic profile (8).

In an article in this issue of *Clinical Chemistry*, Leboulanger et al. (9) have moved the field of iontophoresis a step forward. The work clearly demonstrates, in patients treated for bipolar and schizo-affective disorders, that the amounts of lithium extracted were proportional to the corresponding serum concentrations. Normalization of the lithium extraction flux with that of sodium, which acted as an internal standard, permitted the calibration of the monitoring without the need for a blood measurement. The concentrations of lithium in blood could be predicted.

One could argue that lithium is probably an "ideal" drug for noninvasive monitoring by reverse iontophoresis. Lithium is a non-protein-bound cation and is transported mainly by electromigration. As it is a small ion with high mobility when under an electrical field, it is more efficiently extracted than the above-mentioned organic drugs. Its plasma concentrations are higher than the plasma concentrations of these conventional drugs. However, the innovative demonstration in patients of the potential of reverse iontophoresis for noninvasive drug monitoring opens new doors and holds promise for other patients who require drug monitoring.

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