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Review article

Transdermal reverse iontophoresis: A novel technique for therapeutic drug monitoring

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ABSTRACT

Application of transdermal reverse iontophoresis for diagnostic purpose is a relatively new concept but its short span of research is full of ups and downs. In early nineties, when the idea was floated, it received a dubious welcome by the scientific community. Yet to the disbelief of many, 2001 saw the launching of GlucoWatch® G2 Biographer, the first device that could measure the blood sugar level noninvasively. Unfortunately, the device failed to match the expectation and was withdrawn in 2007. However, the concept stayed on. Research on reverse iontophoresis has diversified in many fields. Numerous *in vitro* and *in vivo* experiments confirmed the prospect of reverse iontophoresis as a noninvasive tool in therapeutic drug monitoring and clinical chemistry. This review provides an overview about the recent developments in reverse iontophoresis in the field of therapeutic drug monitoring.

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1. Introduction

Worldwide trends of healthcare have progressed from generalistic to individualistic therapy, especially in economically advanced countries. However, the practice raises the cost of treatment and only the rich nations can enjoy the benefits of such practice. For the rest of the world, developing as well as underdeveloped, generalized treatment is the only economically sustainable option. Yet, there are some drugs where the risks of treatment without dose titration are dangerously high. Belong to this class are drugs, used for treatment of cancer, epilepsy, depression, and arrhythmia (Table 1).

Therapeutic drug monitoring was introduced in the early 1970s with multiple objectives; improving patient safety, individualizing dosage regimen and minimizing systemic toxicity [1]. In general, drugs showing narrow therapeutic index, concentration related adverse effects and pharmacokinetic variations are considered to be candidate molecules for therapeutic drug monitoring. Unfortunately, the existing method used for therapeutic monitoring is invasive as well as time consuming and often results in poor patient compliance. Extensive research is going on to screen non-invasive methods to develop new techniques for therapeutic drug monitoring. Transdermal reverse iontophoresis is one such method.

Table 1
Drug molecules that require monitoring of plasma concentration.

Categories	Drug molecule	Reason for therapeutic monitoring
Analgesics	Acetaminophen	Narrow therapeutic range (50–250 μg/ml) and potentially toxic at 200 μg/ml
Analgesics	Salicylate	Produce several side effects. Therapeutic window is low (50–250 μg/ml) and potentially toxic at 300 μg/ml
Antianginal	Perhexiline	High inter and intra individual pharmacokinetic variability and narrow therapeutic index
Antiarrhythmic	Amiodarone	Unusual pharmacokinetics. Toxicity and drug interaction are common in long term therapy
Antiarrhythmic	Quinidine	Drug interaction
Antiarrhythmic	Propranolol	Narrow therapeutic index
Antiarrhythmic	Procainamide	Narrow therapeutic index
Antiarrhythmic	Mexilitine	Severe side effects like blurred vision, numbness, and tingling.
Lignocaine	Antiarrhythmic	Toxicity observed even at concentration range as low as 1.5 μg/ml
Antiarrhythmic	Flecainide	Narrow therapeutic range (0.2–1 μg/ml); toxicity observed over concentration 1 μg/ml and very frequent over 1.6 μg/ml
Antiarrhythmic	Disopyramide	Narrow therapeutic range (2.8–7.5 μg/ml)
Antiarrhythmic	Digoxin	Potentially toxic for patients with impaired renal function
Antiarrhythmic	Digitoxin	Displays age related pharmacokinetic variability
Antibiotics	Amikacin	Narrow therapeutic range; causes serious side effects such as nephrotoxicity and ototoxicity
Antibiotics	Chloramphenicol	Low therapeutic index, variable pharmacokinetics and serious side effects
Antibiotics	Kanamycin	Severe adverse effects including nephrotoxicity and ototoxicity.
Antibiotics	Netilmycin	Narrow therapeutic range and associated with serious ototoxicity
Antibiotics	Tobramycin	Narrow therapeutic range
Antibiotics	Vancomycin	Narrow therapeutic range. Irreversible nephrotoxicity
Antidepressants	Lithium	Narrow therapeutic index; severe adverse effects (psychosis, kidney failure, seizures, coma and death)
Antiepileptic	Carbamazepine	Low therapeutic index
Antiepileptic	Ethosuximide	Low therapeutic index
Antiepileptic	Gabapentin	Low therapeutic index
Antiepileptic	Phenobarbital	Narrow therapeutic range (10–35 μg/ml)
Antiepileptic	Phenytoin	Narrow therapeutic range (10–20 μg/ml)
Antiepileptic	Primidone	Neurotoxicity
Antiepileptic	Valproic acid	Narrow therapeutic range (6–22 μg/ml)
Antineoplastics	Methotrexate	Narrow therapeutic index

Transdermal reverse iontophoresis is a needleless technique that can extract biomolecules and drugs through intact skin. It has tremendous potential in the diagnostic branch of medical science [2]. The technique uses a small electric current to drive both charged and uncharged polar moieties across intact skin [3] that hogged much lime light, when it led to the development of the GlucoWatch® G2 Biographer (Cynus Inc., Redwood city, CA) [4]. The device in amalgamation with an autosensor (single use component) was used to check glucose in the body up to 12 h period. The autosensor contained hydrogel disks, iontophoresis electrodes, biosensors, and adhesives to hold it firmly to the skin. Hydrogel disk contained glucose oxidase enzyme and extracted glucose. The biosensor consisted of two parts: a) tranducer, amperometric sensors that monitor current when electrons are exchanged on electrodes b) signal processing system that transfers the signal into a readable form. When the device was worn like a watch and it generated low level of current (300 μA) which affected the subdermal molecules. Under the influence of electric field the positive ions moved towards the cathodal terminal and negative ions moved towards anode. However, glucose being a neutral molecule got affected by the electroosmotic flow and moved towards the cathode. The glucose was extracted into the hydrogel disks that reacted with the enzyme glucose oxidase to form hydrogen peroxide.

$$\mathrm{Gluose}(C_6H_{12}O_6) + O_2 \overset{\text{Glucose-oxidase}}{\rightarrow} \mathrm{Gluconolactone}(C_6H_{10}O_6) + H_2O_2 \quad (1)$$

Hydrogen peroxide was reduced at platinum electrode through the subsequent reaction:

$$H_2O_2 \rightarrow 2H^+ + O_2 + 2e \quad (2)$$

The electrode recognized the number of electrons transported which was proportional to the number of glucose molecules extracted. The resulting current signal was translated into the corresponding blood glucose level through a data translation algorithm [5–6].

However, the device had numerous restrictions such as the need for calibration with a standard blood glucose meter, a warm-up period after calibration, and substitution of disposable pad every 12 h etc. In addition, users developed skin reactions which diminished the suitability of the device. The other severe problem was the shutdown of the device during sweating. Moreover, the company made some incorrect financial decisions which affected the market acceptability of the device. The sale of the device was ceased in 2007, because of incessant problems.

Though, as a device GlucoWatch® G2 Biographer failed to impress its customers, the concept stayed on. Investigations on the reverse iontophoretic methods of therapeutic drug monitoring for a number of drugs are at various stages of progress. The technique is also being investigated to track the subdermal level of indigenous molecules like urea [7], amino acid [1], lithium [2], phenytoin [3], and valproate [4]. Hence a discussion on the technique for therapeutic drug monitoring is well warranted. This article discusses the basic principles as well as recent developments on reverse iontophoresis in the field of therapeutic drug monitoring.

2. Basic features of transdermal reverse iontophoresis

In transdermal reverse iontophoresis, the candidate molecules are extracted through skin (Fig. 1). Hence it is important to understand the barrier properties of skin to understand the concept of reverse iontophoresis [8]. Anatomically the skin can be divided into three major layers (Epidermis, dermis, and subcutis). Epidermis, the outer-most layer can be further subdivided into four distinct strata. Generally, from superficial to deep, these are stratum conrneum, stratum granulosum, stratum spinosum, and stratum basale. However, the