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Review

Transdermal drug pharmacokinetics in man: Interindividual variability and partial prediction

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ABSTRACT

A database of human dermatopharmacokinetic parameters of 12 transdermal patches is established. The effect of system design, application site, and metabolism on pharmacokinetic data is discussed, and interindividual variability of data and its possible sources evaluated. Using multiple regression analysis, two equations based on drugs physicochemical characteristics are suggested for partial prediction of peak plasma concentration (C_{max}) after patch application. Patch application presumably decreases variance as rub-off, wash and exfoliation steps are diminished.

The results showed that interindividual variation, in terms of coefficient of variation (CV) of C_{max}, is inversely correlated with drugs molecular weight and lipophilicity in the range of $200 < MW < 400$ and $1.6 < \log K_{oct} < 4.3$. Multiple regression analysis of C_{max} against physichochemical parameters demonstrated the prominent contribution of hydrogen bonding acceptability of the molecules on their maximal plasma concentration after patch administration.

The findings suggest that the serum concentration profile for transdermal therapeutic systems (TTS) is a net result of the system performance, drug absorption and elimination. Thus, the variability in serum concentration is a function of variability of each process involved. This should be noted in explanation of effect of molecular features of drugs on their plasma concentration profile.

Contents

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1. Introduction

Scopolamine was the first drug marketed as a transdermal therapeutic system (TTS). Incremental design developments resulted in a significant market growth of these products. Their advantages (reduced first pass effect and GI incompatibility, constant therapeutic drug level, and increased patient compliance) have increased their popularity.

Today, numerous drugs have been delivered successfully through transdermal patches: scopolamine, nitroglycerin, nicotine, clonidine, fentanyl, estradiol, testosterone, oxybutynin, and recently methylphenidate, selegiline, rivastigmine and rotigotine.

However, considering the efficient skin barrier properties, specific physicochemical properties are needed for a chemical to be a candidate for passive transdermal delivery. The molecules should be small (MW <500), have a low melting point (<200 °C), and have a log K_{oct} of ~2 (Vecchia and Bunge, 2003).

Predictive equations for skin permeability coefficients of drugs are mainly made based on the in vitro static cell experiments using animal or human skin (Potts and Guy, 1992; Cronin et al., 1999). Detailed analysis of the pharmacokinetics of transdermal drug delivery and its correlation with physicochemical characteristics of the delivered drugs is minimal. Moreover, there is considerable interindividual variation in transdermal penetration and pharmacokinetics, which could be one reason for imprecision in predicting dermatopharmacokinetics parameters of transdermally delivered drugs based on their molecular properties.

This study reviews the dermatopharmacokinetic parameters of the drugs marketed as several brands of transdermal patches, reports the interindividual variations in pharmacokinetics parameters such as C_{max} (maximal plasma concentration), and correlates the in vivo data and physicochemical characteristics of the drugs. Patches were chosen as they minimize the variance from three steps of penetration: rub-off, exfoliation and wash (Wester and Maibach, 1983).

2. Transdermal therapeutic systems (TTS)

Currently, at least 13 drugs are widely marketed as transdermal therapeutic system (Table 1). Each transdermal system was designed according to a therapeutic rationale based on existing pharmacokinetic/pharmacodynamic data.

3. Pharmacokinetic parameters of TTS after single-dose application

The single-dose pharmacokinetic profile for transdermal delivery includes three periods: (1) the time until plasma concentrations are achieved (lag time); (2) the plateau at constant steady-state plasma concentrations; and (3) a declining phase post patch removal.

The last phase may be prolonged due to the presence of a skin depot, and the drugs pharmacokinetic characteristics (Berner and John, 1994; Grond et al., 2000).

TTS pharmacokinetic evaluation is often accomplished through randomized crossover studies, comparing the pharmacokinetic profile of a transdermal system with that of an intravenous or oral dose, or comparing different products for bioequivalence studies.

Plasma concentration time profiles for most of the transdermal systems are characterized in terms of AUC_{0-t} (area under the time concentration curve from time 0 to time t), $AUC_{0-\Phi}$ (area under the time concentration curve from time 0 to infinity), C_{max} (maximal plasma drug concentration) and T_{max} (time to maximal plasma drug concentration). C_{max} occurs due to: (a) slight depletion in driving force of drug; (b) variation due to plasma assay/sampling; and (c) other reasons such as circulation variation. For any of these, C_{max} provides a practical estimate of C_{ss} (plasma concentration at steady state).

Table 2 (2.1 to 2.12) demonstrates the pharmacokinetic data of transdermal patches, after single-dose treatment.

Table 3 (3.1 to 3.5) presents metabolite pharmacokinetic data.

4. Correlation of physicochemistry and plasma concentration of drugs

Scheuplein and Blank, proposed that epidermal penetration depends on the structural features of the penetrant (Scheuplein and Blank, 1971). The epidermal transport of most solutes is restricted to passive diffusion across the stratum corneum. Studies have evaluated the role of molecular structure and physicochemistry in this process. Most attempts to develop predictive equations for permeability have focused on the contributions of molecular size and the solubility in stratum corneum lipids. The data availability, and relative success in addressing a wide range of biophysical processes involved in the skin permeation make molecular weight (MW) and logarithmically transformed octanol–water partition coefficient (log K_{oct}) the most widely used parameters for predicting skin penetration (Vecchia and Bunge, 2003). Melting point may also be considered as an important predictor of skin permeability coefficient as it correlates strongly with oil solubility of drugs (Yalkowsky, 1981; Barratt, 1995).

4.1. Predictive models for skin permeability

Two types of structure–activity models have been used to estimate the skin permeability coefficients of chemicals: empirical and theoretical. Theoretical models are based on the contributions of the possible routes of percutaneous penetration and the interactions of the elements of these routes with the penetrants. Empirical models rely on measured experimental permeability coefficients of series of chemicals and correlate them with the physicochemical properties.

The Guy and Hadgraft theoretical model (Guy and Hadgraft, 1985) is based on a linear pharmacokinetic model. The rate constants in this model have been chosen such that they may be related to the penetrants physicochemical properties. Equations have been derived which may be used predictively to estimate the concentration of drug in the plasma following transdermal application.

A database of in vitro skin permeability coefficient values has been consolidated and over 20 empirical equations have been published estimating permeability coefficients for chemicals penetrating the human skin from aqueous vehicles (Vecchia and Bunge, 2003). One of the most widely used empirical models was developed by Potts and Guy, predicting permeability coefficient (Kp) based on log K_{oct} and molecular weight (MW) (1) (Potts and Guy,