Modelling the formation of a drug reservoir in the stratum corneum and its impact on reverse iontophoretic extraction.

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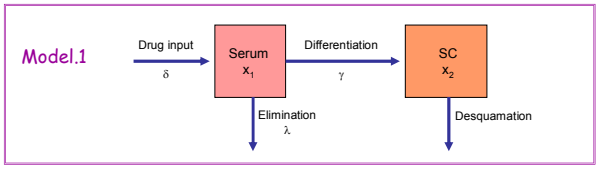
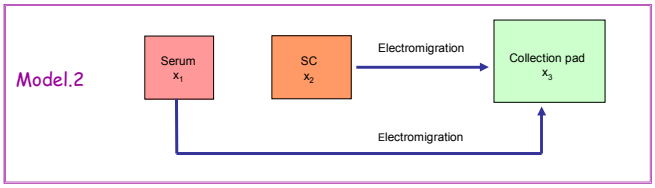
Introduction: The reverse iontophoresis of lithium [1] has shown that (a) large amounts of the drug initially extracted were unrelated to the drug's levels in serum and (b) the fluxes of extraction subsequently decreased and became proportional to the drug serum concentration. It was suggested that during the "warm-up" period, the drug was extracted from a so-called "skin reservoir" which could be located at the stratum corneum (SC) level and builds up during chronic therapy with lithium as followed by bipolar patients.

Objectives: To discriminate the subdermal from the skin contribution to the fluxes of iontophoretic extraction.

Methods: Two related mathematical models were built:





1. Model 1 describes the formation of a Li^+ reservoir in the SC in the course of a multiple dose regimen via the differentiation and ultimate death of viable epidermal keratinocytes into SC corneocytes, and has a timescale of the order of weeks.

Assumptions: Li^+ enters the SC at the rate at which living cells die to form the SC, and is then trapped in the reservoir, being only released when the outer layer of skin is shed in desquamation after approximately two weeks. We assume that no Li^+ is present in either the serum or the SC before the first dose. Combining the above assumptions we obtain the model:

$$\text{(1a)}\quad \frac{dx_1}{dt}(t) = -\lambda\, x_1(t) - \gamma\, x_1(t) + \sum_{i=1}^{N} \delta\, k \exp(-k(t - T_i)) \qquad \text{(1b)}\quad \frac{dx_2}{dt}(t) = \begin{cases} \gamma\, x_1(t) & t \le 14 \\ \gamma\, x_1(t) - \gamma\, x_1(t-14) & t > 14 \end{cases}$$

initial conditions: $x_1(i) = 0 \forall i \in [-14, 0]$, $x_2(0) = 0.$

Where: $x_1(t)$ and $x_2(t)$ are the amounts of Li^+ in serum and in the SC, respectively. $\gamma x_1(t)$ and $\gamma x_1(t-14)$ are the rates with which lithium enters and leaves the SC, respectively, γ is the constant of rate of "lithium movement into the SC" , δ is the daily dose, k is the absorption rate constant, λ is the elimination rate constant, and N and Ti are the number of doses taken and the time at which they were taken.

2. Model 2 describes the iontophoretic extraction of Li^+ from the reservoir and subdermal compartments with a timescale of the order of hours.

Assumptions: Li^+ is primarily transported by electro-migration being Na^+, K^+ and Cl^- the key co- and counter- ion competitors for charge carrying. Li^+ flux can be derived analytically from Faraday's law. Li^+ serum concentration and Na^+, K^+ and Cl^- levels in both compartments are constant over the extraction period. The total body water was taken as volume of distribution for the four ions. All ions are extracted from the same location in the skin reservoir. The aqueous mobility of the i^{th} ion in $cm^2 s^{-1} V^{-1}$ was used and assumed to be constant in both compartments.

$$J_i = \frac{I\, t_i}{F\, z_i} \qquad t_{Li} = \frac{x_{Li} u_{Li}}{x_{Li} u_{Li} + x_{Na} u_{Na} + x_K u_K + x_{Cl} u_{Cl}}$$

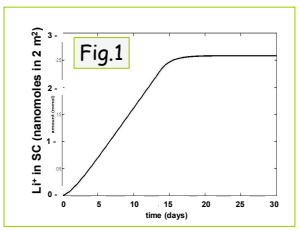
Where: I is the intensity of the current, t_i, z_i and x_i are the transport number, valence and amount of the ion "i" respectively, F is Faraday's constant.

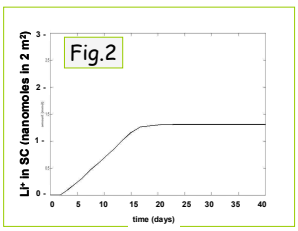
The amount of Li^+ collected on the pad (x_3) will be: $\dfrac{dx_3}{dt} = \dfrac{I}{F} \dfrac{x_2 u_{Li}}{x_2 u_{Li} + x_{Na} u_{Na} + x_K u_K + x_{Cl} u_{Cl}} + \dfrac{I}{F} \dfrac{F_1 u_{Li}}{F_1 u_{Li} + S_{Na} u_{Na} + S_K u_K + S_{Cl} u_{Cl}}$

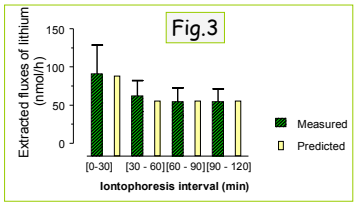
The initial conditions are taken as: $x_2(0) = F_2$, $x_3(0) = 0$

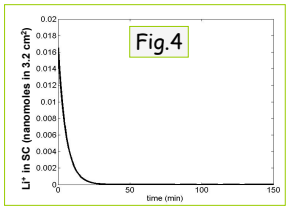
F_1 = amount of Li^+ in serum. F_2 = amount of Li^+ in the SC calculated from the first model and scaled to the amount directly below the collection pad

Results: The amount of Li^+ in the SC increases rapidly upon therapy initiation and achieves a steady state once the drug clearance by the desquamation process is established (Fig.1). A significant effect of persistent non-compliance on the SC reservoir of Li^+ was predicted by the model, Fig. 2 illustrates the case when the patient takes the tablet every other day).









The numerical solution of the iontophoretic model - assuming complete adherence to the dosage regimen and that iontophoresis occurred for 3 hours halfway through the 31st day was successfully compared to previous data [1] on lithium extraction in bipolar patients (Fig.3). Figure 4 shows the depletion of the Li^+ reservoir in the area beneath the collector patch during iontophoresis. These results suggest the models mimic well both the "warm up" and subsequent extraction periods and had used the key parameters playing a role in determining how the SC reservoir is formed and subsequently emptied during reverse iontophoresis.

Conclusions

1. The mathematical model effectively mimicked the warm up period and highlighted the parameters which play a key role in determining the level of the SC reservoir and how it is emptied during reverse iontophoresis.
2. The model suggests that the degree of noncompliance by a patient could be estimated by comparing the data collected during the warm up period with the values expected for a fully compliant individual.

➢ The complete model description will appear shortly in "Computational and Mathematical Methods in Medicine"

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