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International Journal of Pharmaceutics 154 (1997) 229–234

international journal of pharmaceutics

Electrically enhanced transdermal delivery of domperidone

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Received 18 February 1997; received in revised form 6 May 1997; accepted 7 May 1997

Abstract

The aim of this study was to investigate whether transdermal delivery of domperidone can be enhanced to therapeutic levels by iontophoresis and/or electroporation. In vitro studies were performed with a solution of domperidone pH 3.5 in 9.5% (v/v) ethanol. Iontophoresis (2 h at 0.4 mA/cm^2) increased the transdermal permeation by a factor 15 as compared to passive diffusion. Application of 5 long ($\tau = 700$ ms) high-voltage (250 V) pulses increased the domperidone permeation by a factor of up to 70. Application of one pulse (250 V–700 ms) prior to iontophoresis provided similar penetration enhancement to 5 pulses (250 V–700 ms). No significant enhancement was provided by application of one short pulse (1000 V–4 ms) prior to iontophoresis, probably due to a different mechanism of permeabilization and /or recovery kinetics to the initial permeability state. The domperidone permeation flux by skin electroporation (1.5 μg/cm^2 h) is in the range of the fluxes measured with chemical penetration enhancers but the lag time was reduced. However, due to the low hydrosolubility of domperidone, electrically enhanced flux remains too low for therapeutic application. © 1997 Elsevier Science B.V.

Keywords: Domperidone; Transdermal delivery; Iontophoresis; Electroporation

1. Introduction

Drug delivery across skin offers a non invasive, user-friendly alternative to conventional oral or parenteral administrations. Potential degradation in the gastro-intestinal tract or hepatic first pass are avoided. Transdermal therapeutic systems allow sustained and controlled release of drug. However the skin's outer layer, the stratum corneum, is an extremely effective barrier which prevents transport of most drugs at therapeutic rates. Hence, candidates for passive transdermal delivery share three common properties: effectiveness at relatively low doses, molecular mass less than 500 Da and lipophilicity. Lag times of several hours are often observed (Guy and Hadgraft, 1989).

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PII S0378-5173(97)00139-7

Several strategies have been developed to enhance transdermal delivery by modifying skin's barrier properties and/or providing a driving force for drug transport. Both chemical and physical approaches have been explored.

Iontophoresis has been extensively studied. It is a process of enhancing and controlling the penetration of drugs through the skin by the application of a low intensity electrical current as a driving force (Sage, 1993).

More recently, electroporation, the application of high voltage pulses (from about 50 up to a few hundreds volt) across the skin during a fraction of second, has been shown to enhance the transdermal drug permeation. Enhancement factors up to four orders of magnitude have been found for molecules ranging in size from small ions, drugs, dyes to macromolecules (Prausnitz et al., 1993, 1995; Vanbever et al., 1994, 1996a; Bommannan et al., 1994; Zewert et al., 1995; Regnier et al., in press). High voltage pulses are believed to create new aqueous pathways in the stratum corneum, molecular transport occurring through these 'electropores' by electrophoresis and diffusion.

Domperidone (see Fig. 1 for chemical structure and physicochemical properties) is a selective peripheral dopamine antagonist at the D_2 receptor used in prevention and symptomatic relief of acute nausea and vomiting. The transdermal delivery of domperidone could therefore be convenient to avoid oral administration in case of such symptoms. The passive delivery of domperidone was previously investigated (Blanes et al., 1990; Calpena et al., 1994). Despite the use of a penetration enhancer d-limonene in 70% ethanol, the steady state fluxes (11.8 and 7.5 $\mu g/cm^2$ h with and without d-limonene respectively) were considered too low to reach the therapeutic level (18 ng/ml) and the lag time remained very high (on the order of 3.6 and 20 h for rat and human skin respectively).

An alternative to the use of potentially toxic chemical enhancers could be the use of electric current to enhance domperidone permeation. The potential advantages of iontophoresis and/or electroporation over passive diffusion with chemical enhancer could be i) the large enhancement factors reported ii) the rapid delivery with an onset of action of minutes, interesting in the case of nausea iii) a control of the dose delivered iv) a good tolerance for iontophoresis (for review: Sage, 1993; Singh and Maibach, 1996; Smith and Maibach, 1996).

Therefore, the aim of this study was to investigate the transdermal delivery of domperidone by iontophoresis and/or electroporation.

2. Materials and methods

2.1. Chemicals

Domperidone and [H^3] radio-labelled domperidone were a gift from Janssen (Beerse, Belgium). The citric acid used to prepare the buffer (analytical grade) was purchased from UCB (Leuven, Belgium). Ethanol, chlorhydric acid and glucose were obtained from Merck–Belgolabo (Overijse, Belgium).

2.2. Material and procedures

Three cm^2 full thickness abdominal hairless rat skin (from 7 to 11 weeks old; Iops hairless mutant, Iffa Credo, St Germain-les-Arbresles, France) was inserted between the donor and the receptor compartments of the diffusion cell (Vanbever et al., 1994). The receptor compartment (7.5 ml) was filled with isotonized phosphate buffer (pH 7.4, 0.024 M). The donor compartment (1.4 ml) was filled with a solution containing domperidone 1 mg/ml acidified with 2 10^{-3} M HCl, [H^3]-domperidone 1 μCi/ml, ethanol 9.5% v/v and citrate buffer 0.08 M, pH 3.5. Ethanol was added in order to facilitate the drug solubilization. Platinum electrodes (1 cm^2) were connected to the

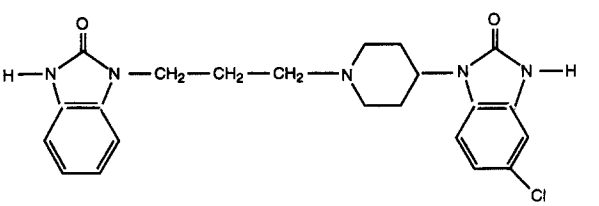

Fig. 1. Chemical structure of domperidone (MW: 426, Koct/water: 8000).

iontophoresis power source or to the electroporation device (Easyject Plus®, Equibio, Seraing, Belgium; Vanbever et al., 1994), the anode being inserted in the donor compartment for both electrical protocols and the cathode in the receptor compartment. The interelectrodes distance was 1 cm. The time interval between the pre pulse and iontophoretic current switching on was a few s. The amount of transferred charges during the pulses was calculated as previously reported (Vanbever and Préat, 1995). Abbreviated descriptions of electrical protocols are given in the paper and can be interpreted according to the following example: $5 \times (250\ \text{V}-700\ \text{ms})$ indicates that 5 pulses were applied with a voltage to the electrodes = 250 V and $\tau = 700$ ms. τ corresponds to the length between the beginning of the pulses and the time when the voltage reaches 37% of its initial value.

The transport of domperidone permeation was followed for 6 hours. The drug concentration was determined by measuring the radioactivity in a liquid scintillation counter. The ratio of the cumulative quantities detected in the receptor compartment to the membrane area was calculated as a function of time. Fluxes were deduced by linear regression. The results are expressed as means ± the standard errors of the means.

The electrochemical stability of domperidone was checked by HPLC (Calpena et al., 1994). Statistical analysis was performed on the cumulative quantities detected at 6 h by a one-way analysis of variance (Anova, Scheffé-F test).

3. Results and discussion

3.1. Iontophoresis

The iontophoretic delivery of ionized domperidone ($pK_a = 7.9$) was first investigated. The cumulative quantity of domperidone was measured during current application (2 h at 0.4 mA/cm²) and 4 h thereafter. Iontophoresis was compared to a passive diffusion performed during 6 h.

As shown in Fig. 2 and Table 1, application of iontophoresis enhanced the transdermal domperidone permeation. The cumulative quantity detected after 6 h passive diffusion (0.064 ± 0.013 μg/cm²) was increased by a factor of 15 (up to 1.068 ± 0.135 μg/cm²) by iontophoresis. Moreover, iontophoresis reduced the lag time to less than 2 h (1.8 ± 0.4 h). The mechanisms responsible for the increased permeation might include electrophoretic movement, electro-osmotic flux and diffusion across skin. The mean permeation flux observed by iontophoresis (Table 1) was low as compared to the fluxes obtained by chemical penetration enhancers (up to 11.8 μg/cm² h for rat skin; Calpena et al., 1994).

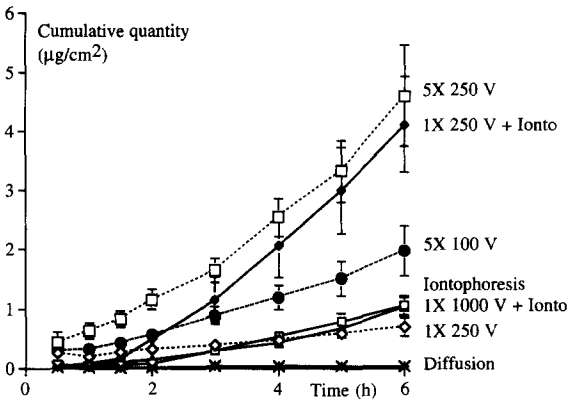

Fig. 2. Cumulative quantity of domperidone detected in the receptor compartment as a function of time. Electroporation—1 or 5×250 V–700 ms ($n = 6$) or 5×100 V–1000 ms ($n = 7$)—was compared to 2 h iontophoresis ($n = 7$) or to electroporation (1×250 V–700 ms ($n = 7$) or 1×1000 V–4 ms ($n = 7$)) followed by 2 hours iontophoresis (0.4 mA/cm²).

3.2. Electroporation

Electroporation has been demonstrated as a powerful method to overcome the stratum corneum barrier (Prausnitz et al., 1993, 1995; Vanbever et al., 1994, 1996a). Therefore, transdermal domperidone delivery was investigated by application of high voltage pulses. 1 or $5 \times (250$ V–700 ms) were applied and compared to the application of $5 \times (100$ V–1000 ms) (Table 1; Vanbever et al., 1994, 1996a).

Application of $5 \times (250$ V–700 ms) significantly enhanced the drug permeation versus passive diffusion and iontophoresis (Fig. 2, Table 1; $p < 0.05$). The domperidone permeation increased up

Table 1
Cumulative quantity (at 6 h), flux (calculated between 4 and 6 h) of domperidone and amount of charges transferred as a function of the electrical treatment

	a Cumulative quantities (ng/cm^2)	*b* Flux (ng/cm^2 h)	*c* Transferred charges (C)	*d* Ratio (*a*/*c*) (ng/cm^2 C)
Diffusion	64 ± 13	N.D.	/	
Iontophoresis (I) 2 h (0.4 mA/cm^2)	1068 ± 135	259 ± 34	8.6	124
Electroporation (EP)				
1 × (250 V–700 ms)	725 ± 154	133 ± 40	0.7	1035
5 × (250 V–700 ms)	4616 ± 858	1494 ± 399	3.6	1282
5 × (100 V–1000 ms)	1986 ± 431	534 ± 190	1.4	1419
EP + I				
250 V + I	4130 ± 809	1130 ± 181	9.3	444
1000 V + I	1064 ± 162	355 ± 39	8.6	124

to a factor 70. Increasing the number of pulses significantly enhanced the drug permeation ($p < 0.05$).

A correlation exists between the amount of charges transferred and the cumulative quantities detected after electroporation (Table 1) indicating that the electrophoretic movement might play an important role in the domperidone transport by electroporation (Regnier et al., in press).

A similar permeation enhancement was observed with 2 h iontophoresis and 1 × (250 V–700 ms). The difference in transferred charges (Table 1) could indicate that domperidone transport was less hindered during electroporation than during iontophoresis, due to changes in skin micro structures, i.e. the creation of new or enlarged pathways (Prausnitz et al., 1995; Bommannan et al., 1994).

After pulsing, the rate of domperidone permeation remained elevated for several hours, suggesting the creation of a drug reservoir within the skin and/or a persistent change in skin permeability due to altered skin structure (Vanbever, 1997). Due to the high partition coefficient of domperidone, a high affinity for the lipophilic environment of the stratum corneum might be responsible for the drug reservoir formation (Jadoul et al., 1995). As reported previously, increased passive diffusion due to a permeabilized state can be observed in vitro for more than 6 h after application of high voltage pulses (Vanbever et al., 1996b). The increased permeability observed after high voltage pulsing has recently been related to a general perturbation of the stratum corneum lipid structure (Jadoul, 1997).

3.3. Electroporation plus iontophoresis

Because electroporation is mechanistically different, involving alterations of skin structure, application of electroporation in combination with other enhancers could be beneficial (Prausnitz et al., 1993). The application of a short high voltage pulse prior to iontophoresis has been shown to enhance iontophoretic transport of LHRH about 10 fold (Bommannan et al., 1994; Potts et al., in press).

Two kinds of electroporation protocols were applied prior to iontophoresis in this study: high voltage-short duration (1000 V–4 ms) and long duration pulses (250 V–700 ms) (Bommannan et al., 1994; Vanbever and Préat, 1995). Results are shown in Fig. 2 and Table 1. A significant enhancement in transdermal drug permeation was observed when 1 × (250 V–700 ms) was followed by 2 h iontophoresis (Fig. 2; $p < 0.05$ versus passive diffusion and one high voltage pulse alone). This increased transport cannot be explained by

incremental charges due to the pulse (Table 1). The creation of a permeabilized state of the skin due to high voltage pulses exposure before iontophoresis is more likely the origin of the synergism between electroporation and iontophoresis. Potts et al. showed that the relative transport enhancement achieved by application of a high voltage pulse prior to iontophoresis decreased with increasing size of the peptide. The results are therefore consistent with the electro-induced formation of ion-conductive pathways of finite average size (Potts et al., in press).

Surprisingly, no significant enhancement of domperidone iontophoretic flux could be seen when $1 \times (1000\ V-4\ ms)$ was applied about 4 s prior to iontophoresis. A two steps phenomenon was suggested in the phenomenon of skin permeabilization by high voltage pulses: i) the permeabilized structure is created due to the high voltage applied and ii) the maintenance and/or extension is dependent on the duration and the number of pulses (Vanbever et al., 1996b). The short pulse could not be able therefore to maintain the permeabilized structure until iontophoresis switching on. Consistent with this hypothesis, no skin alteration measured by X-ray scattering was detected after repeated application of short pulses in contrast to the perturbations observed with long pulses (Jadoul, 1997). Similarly, alterations detected by non invasive bioengineering studies were less important for short pulses than during longer high voltage pulses or iontophoresis (Vanbever et al., in press).

4. Conclusion

This study investigated the transdermal drug delivery of domperidone by electrical current application. Both iontophoresis and electroporation significantly increased the domperidone permeation. Furthermore, the synergy of one high voltage electrical pulse and iontophoresis puts forward an interesting and promising method for transdermal drug delivery enhancement.

Compared to the use of chemical enhancer, domperidone delivery was not improved by iontophoresis and/or electroporation. However, the potential advantages of electrically enhanced delivery i.e. rapid delivery and control of the dose delivered, confirm the interest of the physical methods to enhance drug delivery.

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