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On the selection of an opioid for local skin analgesia: Structure-skin permeability relationships

Umberto M. Musazzi [a], Carlo Matera [a], Clelia Dallanoce [a], Federica Vacondio [b], Marco De Amici [a], Giulio Vistoli [a], Francesco Cilurzo [a,*], Paola Minghetti [a]

[a] Department of Pharmaceutical Sciences, Università degli Studi di Milano, Via L. Mangiagalli 25, 20133 Milano, Italy
[b] Department of Pharmacy, Università degli Studi di Parma, Parco Area delle Scienze 27/A, 43124 Parma, Italy

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ABSTRACT

Recent studies demonstrated that post-herpetical and inflammatory pain can be locally managed by morphine gels, empirically chosen. Aiming to rationalize the selection of the most suitable opioid for the cutaneous delivery, we studied the *in vitro* penetration through human epidermis of eight opioids, evidencing the critical modifications of the morphinan core. Log *P*, log *D*, solid-state features and solubility were determined. Docking simulations were performed using supramolecular assembly made of ceramide VI. The modifications on position 3 of the morphinan core resulted the most relevant in determining both physicochemical characteristics and diffusion pattern. The 3-methoxy group weakened the cohesiveness of the crystal lattice structure and increased the permeation flux (*J*). Computational studies emphasized that, while permeation is essentially controlled by molecule apolarity, skin retention depends on a fine balance of polar and apolar molecular features. Moreover, ChemPLP scoring the interactions between the opioids and ceramide, correlated with both the amount retained into the epidermis (Q_{ret}) and *J*. The balance of the skin penetration properties and the affinity potency for μ-receptors evidenced hydromorphone as the most suitable compound for the induction of local analgesia.

1. Introduction

Opioids are widely used in pain relief therapies associated with degenerative diseases or neoplastic pathologies. Indeed, WHO guidelines have indicated in systemic opioid administration a first line treatment to control moderate to severe pain (Santini et al., 2013). The discovery of peripheral opioid receptors and their role in mediating analgesia in patients with various types of pain (*e.g.*, chronic rheumatoid arthritis, oral mucositis, bone pain, complex regional pain syndrome after dental, laparoscopic, urinary bladder and knee surgery) raised interest in potential novel applications of opioid receptor drugs (Sawynok, 2014). In particular, the expression of opioid receptors on dermal and epidermal nerve fibers (Ständer et al., 2002) provided the bases for recent clinical studies for evaluating their efficacy in managing post-herpetical pain (Zur, 2014) and inflammatory pain in wounds (Graham et al., 2013). Further investigations seem to confirm the clinical usefulness of locally-applied opioids even though the results are not always robust, and, to some extent, contradictory, especially concerning the skin wounds (Farley, 2011). Among the factors affecting the reproducibility of the results, it is noteworthy the small and heterogeneous patient groups involved in the studies, the inhomogeneity of the locally-applied opioids and, more importantly, the patient's comorbidities that make the estimation of the direct pharmacological effect on skin pain difficult (Welling, 2007; Zaslansky et al., 2014). Besides such clinical reasons, the lack of unequivocal data about the skin penetration and retention of opioids does not permit a rational choice for their clinical use. For example, several studies reported the clinical efficacy of morphine gels even though its choice has been rather empirical since no extensive studies on its dermopharmacokinetic profile are at present available. As a matter of fact, the few related reports were focused on the selection of opioids able to permeate the stratum corneum barrier and reach the systemic circulation (Roy and Flynn, 1989), as exemplified by studies on morphine (Zeppetella et al., 2003), fentanyl (Lane, 2013) or buprenorphine (Evans and Easthope, 2003). When the induction of local analgesia by application of an opioid on the skin is considered, the attention

* Corresponding author. Tel.: +39 250324635; fax: +39 250324657.
E-mail address: francesco.cilurzo@unimi.it (F. Cilurzo).

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should focus on the skin retention, while the often reported skin penetration should be seen as a negative feature, being seemingly related to induced systemic adverse effects. In other words, the rational choice of an opioid for skin analgesia should involve a drug with the highest retention in the epidermis and the lowest permeation through the skin for minimizing the side effects of potential systemic absorption. Furthermore, the selection should take into account the binding potency to the opioid receptors located in the epidermis (Bigliardi et al., 2009).

Aimed at rationalizing the selection of suitable morphine derivatives for local pain relief therapy, the present study analyzed the *in vitro* penetration through as well as the *in vitro* retention in human epidermis of a homogeneous set of opioid drugs, whose analgesic properties are well documented. As reported in Fig. 1, we chose morphine **1**, codeine **5** and six structural analogues, *i.e.*, the morphine-related **2**–**4** and the codeine-related **6**–**8** derivatives. Our experimental results aimed also at uncovering possible predictive descriptors for epidermis retention of drugs. Although various approaches have been proposed for modeling the skin permeation (Mitragotri et al., 2011), the prediction of drug retention into the skin has been poorly investigated so far. To this end, we performed docking simulations between the tested derivatives and a supramolecular assembly made of ceramide VI, with a view to tackling such a prediction as a sort of host-guest model. Ceramide VI was selected since it is the most abundant ceramide of the skin, along with ceramide II, and has been exploited to model the organization of the stratum corneum lipidic network (Minghetti et al., 2003; Wertz and van den Bergh, 1998).

2. Materials and methods

2.1. Materials

Morphine hydrochloride, codeine phosphate, dihydrocodeine bitartrate and oxycodone hydrochloride were purchased from SALARS SpA (Como, Italy). HPLC-grade acetonitrile and MeOH were purchased from VWR International PBI s.r.l. (Milan, Italy). Standard KOH (0.5 M) and HCl (0.5 M) were prepared from Titrisol volumetric vials purchased from VWR International PBI s.r.l. (Milan, Italy). All other reagents and solvents were purchased from Sigma–Aldrich Srl (Milan, Italy) and used without further purification.

2.2. Preparation and characterization of the opioid drug substances

Chemical reaction progress was monitored by TLC analyses performed on commercial silica gel 60 F254 aluminum sheets (Merck KGaA, Darmstadt, Germany); spots were visualized by UV detection and further evidenced by spraying with a dilute alkaline potassium permanganate solution or phosphomolybdic acid in EtOH solution (10%), and the Dragendorff reagent. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Mercury 300 (^{1}H, 300.063; ^{13}C, 75.451 MHz) spectrometer at 20 °C; the deuterated solvents were indicated for each compound. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. ESI-MS spectra were obtained on a Varian 320 LC–MS/MS instrument; data are reported as mass-to-charge ratio (m/z) of the corresponding positively charged molecular ions.

2.2.1. Morphine [(5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol, *1*]

Commercially available morphine hydrochloride (1.000 g, 3.108 mmol) was dissolved in Na_2CO_3 aq. sat. and vigorously extracted with $CHCl_3$/*i*PrOH (9:1, 50 mL × 5). The organic phases were collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a viscous yellow oil, which was recrystallized from Et_2O to give pure morphine base (**1**). Yield: 0.822 g (93%); colorless solid. ^{1}H NMR, ^{13}C NMR and MS spectra were identical to those reported in the literature (Koizumi et al., 2010).

2.2.2. Dihydromorphine [3,6-dihydroxy-(5α,6α)-4,5-epoxy-17-methylmorphinan, *2*]

A stirred suspension of morphine hydrochloride (1.031 g, 3.204 mmol) and 10% Pd/C (50 mg) in MeOH (25 mL) was evacuated and hydrogenated under pressure (50 psi) in a Parr apparatus for 4 h. The reaction mixture was then passed through a pad of Celite® and the filtrate was concentrated under reduced pressure. This crude material was dissolved in $NaHCO_3$ aq. sat. and extracted with $CHCl_3$/*i*PrOH (9:1, 30 mL × 5); the organic phases were collected, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a yellow oil which was recrystallized from CH_3CN to give pure dihydromorphine (**2**). Yield: 0.830 g (90%); pale yellow solid. R_f = 0.23 (CH_2Cl_2/MeOH = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66 (d, 1H, J = 8.0 Hz), 6.55 (d, 1H, J = 8.0 Hz), 4.60 (d, 1H, J = 5.2 Hz), 4.00 (m, 1H), 3.15 (m, 1H), 2.97 (d, 1H, J = 18.4 Hz), 2.59 (dd, 1H, J = 12.4, 3.8 Hz), 2.42 (s, 3H), 2.40 (dd, 1H, J = 18.4, 6.0 Hz), 2.28 (m, 2H), 1.95 (dt, 1H, J = 12.4, 5.2 Hz), 1.69 (ddd, 1H, J = 12.4, 3.8, 1.9 Hz), 1.45 (m, 3H), 1.08 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 146.03, 137.98, 130.07, 125.19, 117.98, 116.69, 89.94, 66.11, 58.92, 46.03, 42.77, 42.01, 38.19, 37.25, 25.61, 19.61, 19.48 ppm; ESI-MS: m/z $[M+H]^+$ calcd for $[C_{17}H_{22}NO_3]^+$ 288.16, found 288.1. ^{1}H NMR, ^{13}C NMR and MS spectra were identical to those reported in the literature (Przybyl et al., 2003; Varadi et al., 2011).

2.2.3. Oxymorphone [4,5-α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one, *3*]

This compound was synthesized from commercially available oxycodone hydrochloride following a procedure already reported in the literature (Kvernenes et al., 2007). Yield: 0.799 g (93%) from

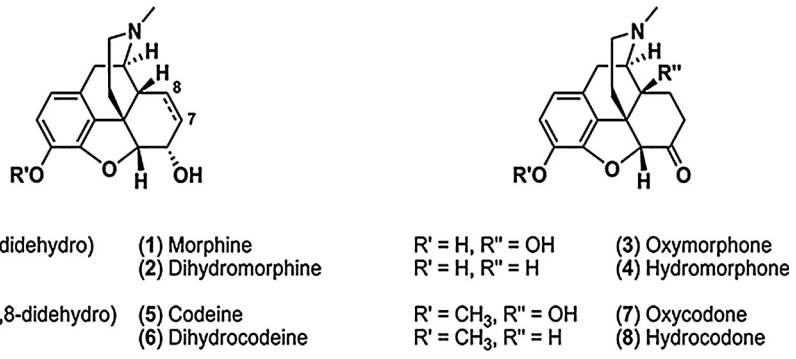

Fig. 1. Structures of the opioid drug substances investigated in this study.