



Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Topically applied mesoridazine exhibits the strongest cutaneous analgesia and minimized skin disruption among tricyclic antidepressants: The skin absorption assessment



Kuo-Sheng Liu^a, Yu-Wen Chen^{b,c}, Ibrahim A. Aljuffali^d, Chia-Wen Chang^e, Jhi-Joung Wang^{c,*}, Jia-You Fang^{e,f,g,h,*}

^a Department of Pharmacy, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

^b Department of Physical Therapy, China Medical University, Taichung, Taiwan

^c Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan

^d Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

^e Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Kweishan, Taoyuan, Taiwan

^f Chinese Herbal Medicine Research Team, Healthy Aging Research Center, Chang Gung University, Kweishan, Taoyuan, Taiwan

^g Department of Anesthesiology, Chang Gung Memorial Hospital, Kweishan, Taoyuan, Taiwan

^h Research Center for Industry of Human Ecology, Chang Gung University of Science and Technology, Kweishan, Taoyuan, Taiwan

ARTICLE INFO

Article history:

Received 30 December 2015

Revised 29 May 2016

Accepted in revised form 30 May 2016

Available online 31 May 2016

Keywords:

Tricyclic depressant

Mesoridazine

Skin

Topical delivery

Neuropathic pain

ABSTRACT

Tricyclic antidepressants (TCAs) are found to have an analgesic action for relieving cutaneous pain associated with neuropathies. The aim of this study was to assess cutaneous absorption and analgesia of topically applied TCAs. Percutaneous delivery was investigated using nude mouse and pig skin models at both infinite and saturated doses. We evaluated the cutaneous analgesia in nude mice using the pinprick scores. Among five antidepressants tested in the *in vitro* experiment, mesoridazine, promazine and doxepin showed a superior total absorption percentage. The drug with the lowest total absorption percentage was found to be fluphenazine (<7%) either at an infinite dose or at saturated solubility. The follicular pathway was important for mesoridazine and promazine delivery. Mesoridazine showed stronger skin analgesia than the other TCAs although the *in vivo* skin absorption of mesoridazine (0.34 nmol/mg) was less than that of promazine (0.80 nmol/mg) and doxepin (0.74 nmol/mg). Mesoridazine had a prolonged duration of pain relief (165 min) compared to promazine (83 min) and doxepin (17 min). The skin irritation test demonstrated an evident barrier function deterioration and cutaneous erythema by promazine and doxepin treatment, whereas mesoridazine caused no obvious adverse effect by topical application for up to 7 days.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Neuropathic pain is defined as the pain produced by a lesion or disease of the somatosensory systems [1]. The predominant occurrence of neuropathic pain is the disorder leading to a dysfunctional sensory condition, which affects >8% of the population [2]. This kind of pain largely influences the health-related quality of life with conditions such as depression, fatigue, reduced mobility, sleep disturbance, weight loss, and inability to work. It also causes

substantial costs to society, raising a serious public health concern [3]. Peripheral neuropathic pain is the primary type of nerve-system injury. Damage to periphery tissues or nerves can elicit keratinocytes and vessels in the skin to release substance P, prostaglandins and calcitonin gene-related peptides. These excitatory factors bind to the receptors on nociceptive fibers, generating depolarization [4]. Several diseases, including diabetic neuropathy, postherpetic neuralgia, chemotherapy-induced peripheral neuropathy, radiation dermatitis, bullous dermatoses and hidradenitis suppurativa, can induce the skin pain. Peripheral pain is becoming the most common ailment that motivates patients to seek professional care.

Currently, the first-line treatments for peripheral neuropathic pain are tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors, and anticonvulsants. TCAs

* Corresponding authors at: Department of Medical Research, Chi Mei Medical Center, 901 Chung-Hwa Road, Yungkuang, Tainan 710, Taiwan (J.-J. Wang). Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, 259 Wen-Hwa 1st Road, Kweishan, Taoyuan 333, Taiwan (J.-Y. Fang).

E-mail addresses: 400002@mail.chimei.org.tw (J.-J. Wang), fajy@mail.cgu.edu.tw (J.-Y. Fang).

have been employed as antipsychotic drugs for >60 years. They are also known to possess local anesthetic activity, showing analgesic properties when used topically [5]. The peripheral analgesic effect of TCAs can be attributed to the blockade of the sodium channel and the decrease of cyclic AMP via adenosine receptor activation [6]. An ideal aspect of topical TCAs is the maximization of the local concentration in peripheral effector sites and minimization of the serum level for providing safe administration [7]. TCAs such as amitriptyline are found to be more potent than lidocaine/prilocaine cream (EMLA) in alleviating cutaneous pain [8].

Although some therapies are used for resolving neuropathic pain clinically, patients usually do not respond adequately to drug treatment, and the pain is therefore refractory. The topical delivery is restrained due to the short duration of the analgesic effect [9]. No more than 40–60% of patients with local pain achieve lasting and partial pain relief [10]. Besides doxepin and amitriptyline, only a few options are available for clinical use in local pain control. We aimed to examine the skin absorption and local anesthetic effect of some TCAs to find new candidates for cutaneous analgesia. To our knowledge, no literature reports the permeability of TCAs into/ across the skin. The three TCAs, mesoridazine, promazine, and fluphenazine structurally belonging to phenothiazines, were selected as the permeants in the present work (Fig. 1). The strong analgesic activity of phenothiazine-type TCAs was reported previously [11]. The cutaneous absorption of phenothiazines was evaluated by *in vitro* Franz cell for comparison with doxepin and amitriptyline, the commercially available TCAs for topical application. Different substituents are attached at the 2- and 10-position of the phenothiazine ring. Doxepin and amitriptyline are the antipsychotics with a seven-member ring. The difference in the structure between the two TCAs is an oxygen in the ring of doxepin. The skin retention of the permeants was also determined *in vivo* in the nude mouse. The cutaneous analgesic activity and duration of the topically applied TCAs were also evaluated *in vivo*. Skin irritation such as redness and burning can be observed after topical administration of TCAs at a high concentration [12]. The possible irritation produced by

the drugs was explored by detecting transepidermal water loss (TEWL) and the erythema index.

2. Materials and methods

2.1. Materials

Mesoridazine besylate and promazine hydrochloride were standard references from U.S. Pharmacopeia (Rockville, MD, USA). Fluphenazine dihydrochloride, doxepin hydrochloride and amitriptyline hydrochloride were purchased from Sigma-Aldrich (St. Louis, MO, USA). A cellulose membrane with a molecular weight (MW) cutoff of 6000–8000 Da was supplied by Membrane Filtration Products (Seguin, TX, USA).

2.2. Production of the base form from TCA salts

The base form of TCA salts was obtained by using the precipitation method. After a NH_4OH /water solution (pH = 9) was pipetted by drops into TCA salt in methanol, the base form was precipitated. This precipitate was filtered and washed with water for expelling NH_4OH . The TCA bases were verified by infrared and nuclear magnetic resonance analyses after drying.

2.3. *n*-Octanol/water partition coefficient ($\log P$)

TCAs (0.5 mg) in methanol were pipetted into the test tube, followed by methanol evaporation with nitrogen gas. The *n*-octanol and water (1 ml of each) were mixed in the tube and then stoppered and agitated for 24 h. The *n*-octanol and water phases were withdrawn to quantify TCAs by high-performance liquid chromatography (HPLC). The organic phase was diluted by acetonitrile before the assay.

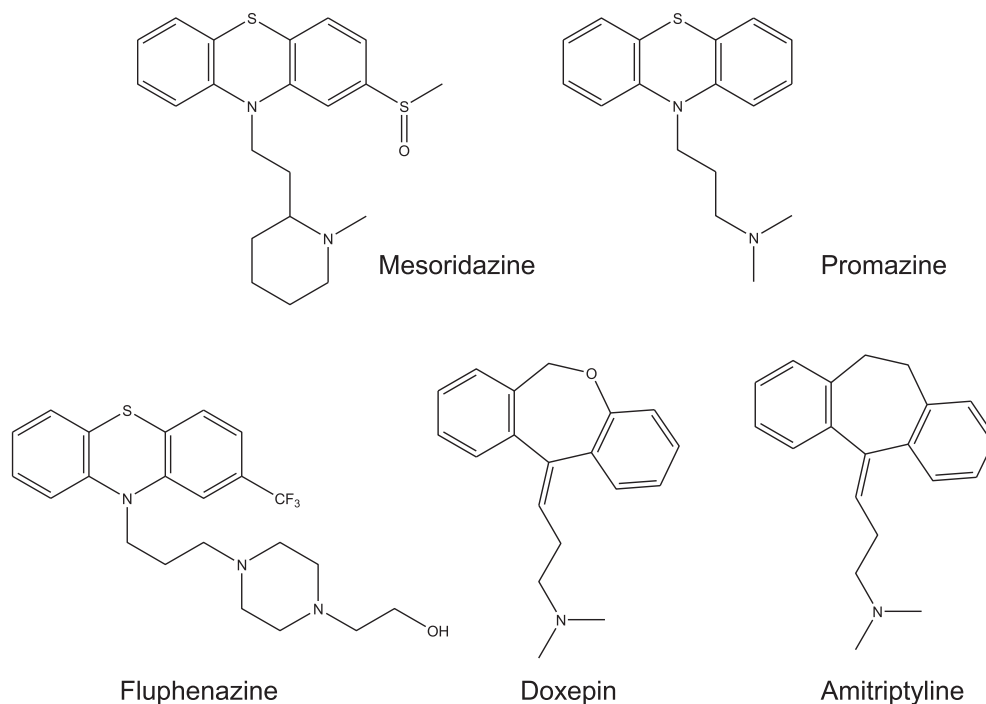


Fig. 1. The chemical structures of mesoridazine, promazine, fluphenazine, doxepin, and amitriptyline.

Download English Version:

<https://daneshyari.com/en/article/2083237>

Download Persian Version:

<https://daneshyari.com/article/2083237>

[Daneshyari.com](https://daneshyari.com)