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Pharmacokinetics and Skin Tolerability of Intracutaneous Zolmitriptan Delivery in Swine Using Adhesive Dermally Applied Microarray

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ABSTRACT

Adhesive Dermally Applied Microarray (ADAM) is a new drug-delivery system that uses microprojections (340-μm long) for intracutaneous drug self-administration. We formulated zolmitriptan, a well-accepted and commonly used migraine medication, for administration using ADAM. *In vivo* studies were conducted in female prepubescent Yorkshire pigs using ADAM 1.9-mg zolmitriptan applied to the inner thigh and left in place for 1 h. Pharmacokinetic studies showed that the ADAM 1.9-mg zolmitriptan was delivered with high efficiency (85%) and high absolute bioavailability (77%). Furthermore, *in vivo* evaluation showed a rapid systemic absorption with a median T_{max} of 15 min. Skin biopsies of the treatment sites showed a mean depth of microprojection penetration of 105.4 ± 3.6 μm. Mass spectrometry imaging showed that the zolmitriptan after 1 h of patch wear time was predominantly localized to the dermis. ADAM zolmitriptan was well tolerated with a transient mild-to-moderate erythema response. The findings in these studies, particularly the rapid zolmitriptan absorption profile after intracutaneous administration, provided validation to advance ADAM zolmitriptan development.

Introduction

Migraine is a common condition characterized by regular episodes of moderate-to-severe headache, along with a range of neurological, gastrointestinal, and autonomic symptoms such as nausea, vomiting, aura, phonophobia, and photophobia.[1,2] For debilitating migraine, serotonin 5-HT1B/1D receptor agonists (triptans) are recommended as first-line therapies.[3,4] In the United States, triptans are available as oral tablets, orally disintegrating tablets, nasal sprays, nasal powders, and in forms for subcutaneous delivery. Although oral formulations are convenient, absorption is considerably slower than that for parenteral administration, which may be further exacerbated by migraine-associated gastrointestinal dysmotility experienced by many patients. Slower absorption delays time to relief, which is a key factor patients consider to be important.[5-7] Conversely, although subcutaneous and intranasal administrations allow for more rapid absorption, some patients are averse to the use of needles and find triptan nasal formulations unpalatable.

Adhesive Dermally Applied Microarray (ADAM) is a new drug-delivery system for intracutaneous drug self-administration (Fig. 1). It consists of a 5-cm^2 adhesive backing onto which is mounted a 3-cm^2 array of 1987 drug-coated, 340-μm-long microprojections. ADAM is applied using a reusable applicator that ensures a consistent force is exerted across users and applications. Upon application, the microprojections are designed to penetrate the uppermost layers of the skin, the stratum corneum and epidermis, allowing the drug to be reconstituted in the interstitial fluid, diffused into the dermis, and systemically absorbed.

There is currently no approved transdermal triptan patch on the market. As of June 2016, Zecuity®, the only approved and marketed triptan (sumatriptan) patch was removed by the manufacturer Teva Pharmaceuticals. Teva voluntarily suspended sales, marketing, and distribution of Zecuity® due to postmarketing reports of application-site reactions including "burn(s) and/or scar(s)." Marketed in 2015 to treat acute migraine headaches in adults, Zecuity® is a single-use and

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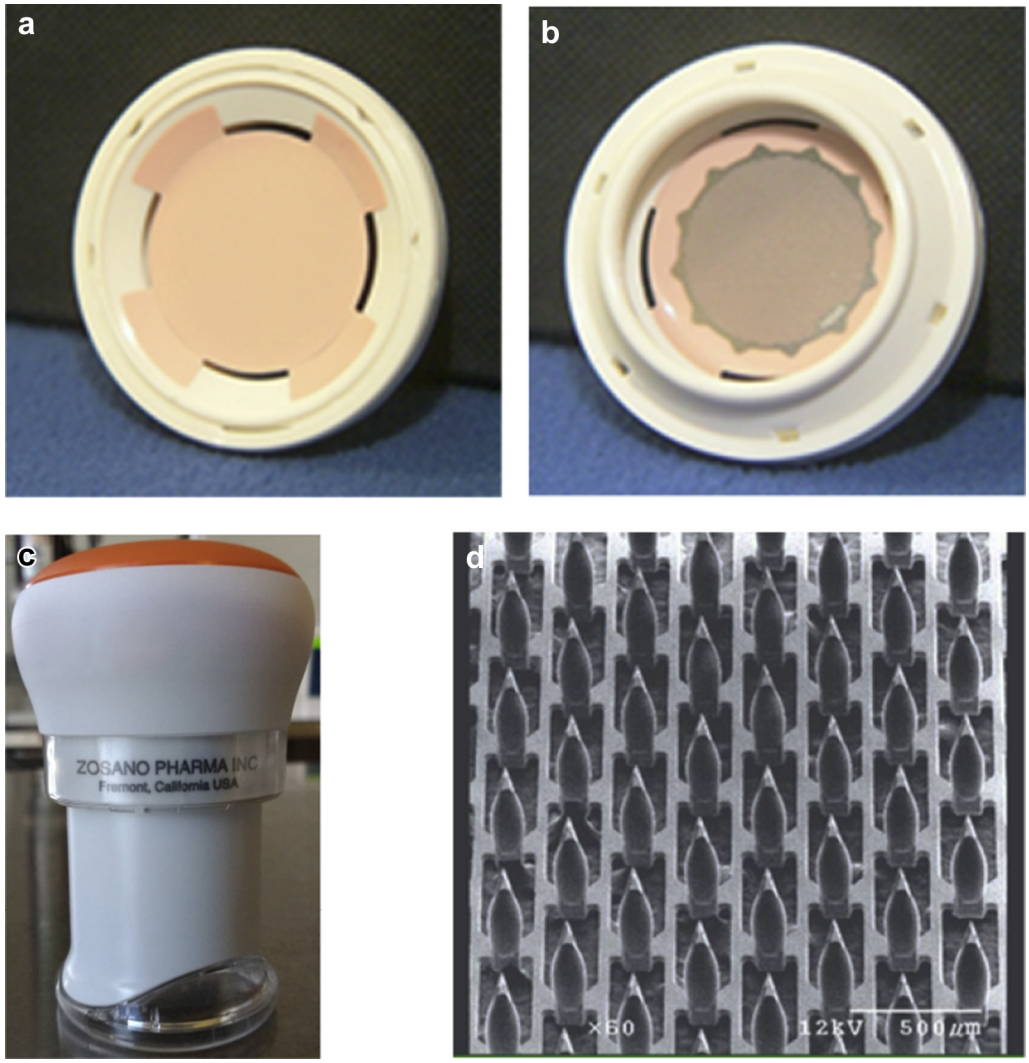

Figure 1. The ADAM drug-delivery system. The 5-cm^2 ADAM configuration showing (a) the top surface, (b) the skin-facing surface, (c) the applicator, and (d) a scanning electron micrograph of zolmitriptan-coated microprojections.

battery-powered sumatriptan (86-mg loading dose) iontophoretic transdermal system which delivers 6.5 mg of sumatriptan over 4 h. Zecuity® is administered to the upper arm or thigh and has a median T_{max} of 1.1 h and mean C_{max} of 22 ng/mL.[8]

We have developed formulations of zolmitriptan, a well-accepted and commonly used migraine medication, for administration using ADAM. Here, we report on the depth of microprojection penetration, localized diffusion, pharmacokinetics (PKs), and skin tolerability of zolmitriptan administered intracutaneously in Yorkshire swine using this innovative technology.

Methods

Prepubescent female Yorkshire swine were used as an animal model. In all studies, ADAM 1.9-mg zolmitriptan or noncoated ADAM were applied to the shaved and cleaned ventral inner thigh of the swine using a hand-held reusable applicator (total energy = 0.26 Joules). The ADAM 1.9-mg zolmitriptan was attached to the applicator, and the applicator was pressed on the skin, releasing the patch and applying it with a predetermined force using a previously described method.[9] The ADAM 1.9-mg zolmitriptan was left in place on the skin for 1 h and then was removed.

Studies were conducted at contract research organizations with approval from their Institutional Animal Care and Use Committee, Preclinical Medevice Innovations (San Carlos, CA).

Depth of Penetration

Punch biopsies (8-mm diameter) were collected from the administration sites immediately after patch removal in 4 animals. Each biopsy was collected from the center of the application site, and up to 8 biopsies were obtained for each ADAM treatment group. Biopsies were fixed in formalin, serially sectioned (5-10 μm), and hematoxylin and eosin (H&E) stained. The depth of penetration (DOP) was measured by a pathologist; measurements were taken from the top of the epidermis to the deepest point of the penetration site using morphometric software (SPOT Image Capture Software, version 5.2). Localized cellular disruption and cellular infiltrations were also evaluated.

Localized Zolmitriptan Distribution in Skin

Four punch biopsies (diameter, 5 mm) were collected from 2 animals that were administered ADAM zolmitriptan and flash-