Introduction

There is no such thing as pain without a brain. Although painful conditions such as central post-stroke pain may exist, in which the mechanisms of the pain essentially lie entirely within the brain, most commonly encountered pain syndromes including post-herpetic neuralgia (PHN), chronic low back pain, and osteoarthritis result from peripheral and likely central nervous system mechanisms. The term topical analgesic has been used to describe analgesics that are applied locally and directly to painful areas; their sites of action are local to the site of application. The term topical analgesic suggests the primary site of action of an analgesic and helps to distinguish it from a transdermal analgesic, which in contrast requires a systemic concentration to be effective. In some instances, analgesics have been considered as “topical” agents, even when formal studies to demonstrate a lack of systemic activity have not been completed. The term targeted peripheral analgesic also suggests a peripheral mechanism of action and may replace the term topical analgesic. Although the mechanism of action of a targeted peripheral analgesic and of topical analgesics may be largely within the peripheral nervous system, their effect on peripheral processing of pain transmission actually may lead to the reduction of central pain mechanisms. If less pain-producing information arrives from the periphery for central processing, it is likely that fewer central mechanisms will be activated. The purpose of this article is to review the use of topical analgesics in the treatment of various painful conditions [1].

That a topical analgesic’s pharmacological activity is directed locally to the site of application as opposed to systemically or intrathecally (as with systemic or intraspinal analgesics) helps to minimize the risks of significant adverse effects and drug-drug interactions [2]. Localized reactions such as rash may occur, but are not commonly experienced [3]. The use of a topical analgesic does not result in a significant systemic concentration of the analgesic in contrast to the use of oral analgesics or a transdermal preparation such as the fentanyl patch. Consequently, consistent use of a true topical analgesic should not result in any significant systemic accumulation of the respective agent. Of the commercially available topical analgesics approved by US Food and Drug Administration (FDA), the 5% lidocaine patch has been studied most extensively. The tolerability and safety of continuous 24-hour use of four lidocaine 5% patches was assessed in one study. Measured plasma lidocaine levels remained below those associated with interference with cardiac activity and no significant systemic side effects were experienced. The same acceptable safety and tolerability was demonstrated in this study regardless of whether the subject used the patch for 12 or 24 hours each day [4]. Patients with chronic low back pain were treated safely with four lidocaine 5% patches every 24 hours for extended periods of time in a separate study [5]. In addition to the safety documented in each of these studies, analgesia (pain relief) was achieved with extended use of the lidocaine 5% patch without anesthesia. No significant dermal sensitivity reactions were experienced in either study [4,5].

However, one should realize that not all topical analgesics are created equally with regard to adverse effects and certain adverse reactions may be unique to the particular analgesic. For example, on application of topical capsaicin, severe burning of the skin at the site of application has been reported to occur in almost 80% of treated patients. Although this drug, when applied topically in its available forms, does not result in significant systemic accumulation or in any life-threatening outcomes and although the incidence of burning may decrease with repeated use, the frequent occurrence of this side effect may negatively impact patient compliance and, as a result, may hinder a patient’s ability to benefit from it [6].
One characteristic of topical analgesics, the lack of drug-drug interactions, may be of great importance for a patient who also is using systemic medications concurrently for other medical conditions. A good example of this situation would be an 80-year-old patient who is taking a number of medications for different medical conditions such as diabetes or hypertension and also is in need of treatment for a chronic pain problem (e.g., PHN or osteoarthritis) [7]. Assuming equal efficacy, the use of a topical analgesic in this setting may be superior to a systemic agent because of the lack of drug-drug interactions. Another advantage of the use of a topical analgesic is that it does not require dose titration often, making these relatively easy drugs to use.

In this era of frequent “off-label” use of various medications, the use of topical analgesics poses an even greater challenge. When using a topical analgesic, one must distinguish between those that are commercially available from those that may be manufactured on a case-by-case basis by a specialized pharmacy. Not all of the topical analgesics that are in use are commercially available products and for years many health care providers have used compounding pharmacies to obtain such agents through other means. This article reviews the use of the topical agents that are commercially available or those for which there is clear evidence that they were manufactured in a consistent and reliable manner. For many compounding pharmacies, there is no proof of such quality control or consistency from one batch to another. Nevertheless, one should realize that compounded, non-commercially available agents are prescribed as topical agents quite often. In one survey of members of the American Society of Regional Anesthesia and Pain Medicine, 27% of the responders indicated that they prescribed such an agent and 47% indicated that they thought that their patient responded favorably to the agent prescribed [8]. There appears to be increasing interest in the development of new topical analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, capsaicin, local anesthetics, antidepressants, glutamate receptor antagonists, α-adrenergic receptor agonists, adenosine, cannabinoids, cholinergic receptor agonists, γ-aminobutyric acid agonists, prostanoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor are each being considered as potential topical analgesics [9].

The mechanism of action of each topical analgesic depends on the specific analgesic. For example, capsaicin-containing topical analgesics appear to achieve their action through their interaction with the VR1 receptor on C and Aδ fibers [10]. This in turn leads to the release of substance P and calcitonin gene-related peptide. Repeated topical application of capsaicin generally is required over several weeks to achieve a therapeutic response. This depletion of substance P in C-fibers has been hypothesized to lead to diminished peripheral and central excitability, resulting in less pain through reduced afferent input [6,10]. Data from histopathological examinations of human nerve biopsies and from animal studies have suggested that application of capsaicin may lead to the degeneration of nerve fibers in the skin underlying the application site. Some have hypothesized that a neurodegenerative effect of capsaicin can be considered one of its mechanisms of analgesia [11]. The mechanism of action of an NSAID is most likely through the inhibition of prostaglandin synthesis and its resulting reduction of inflammation, which have been considered important mechanisms of action for this group of topical analgesics; however, because the extent of the anti-inflammatory effect does not always correlate with the degree of analgesia experienced, other mechanisms of action may be relevant and are under investigation [12]. The antinociceptive effects of topical morphine have been shown to be enhanced by a topical cannabinoid in a recent study in rats in which the radiant tail-flick test was used [13].

The most commonly studied mechanism of the analgesic action of local anesthetic agents appears to be related to the ability of these agents to suppress the activity of peripheral sodium channels within sensory afferents. This results in the reduction of ectopic, paroxysmal discharges and ultimately pain transmission. Reduced expression of mRNA for certain types of sodium channels after local anesthetic use also has been reported [1,3]. However, not all topical local anesthetic agents are the same. As mentioned previously, the lidocaine 5% patch is able to produce its analgesic effect without causing anesthesia; in contrast, the use of EMLA cream (eutectic mixture of local anesthetics, 2.5% lidocaine/2.5% prilocaine; AstraZeneca, Wilmington, DE) may result in analgesia and anesthesia where it is applied. For certain acute painful states (e.g., venipuncture, lumbar puncture, intramuscular injections, and circumcision), this dual effect of EMLA cream actually may be desirable, but perhaps in other settings, it would not [3]. Therefore, choosing which analgesic to use would depend on the clinical setting. The use of the lidocaine 5% patch is not associated with significant anesthesia; therefore, it would not be appropriate to use this preparation for this purpose before procedures. On the other hand, compared with EMLA cream, a separate and unique mechanism of action of the lidocaine 5% patch as a topical analgesic is that the patch itself may help to reduce the allodynia (seen especially with neuropathic pain states such as PHN) by protecting the skin [1].

Antidepressants are commonly used for the management of various chronic pain states as systemic agents; however, their potential as topical analgesics is just beginning to be evaluated. The tricyclic antidepressants are considered “dirty” because they are known to have multiple mechanisms of action; their effect as sodium channel antagonists is now being widely investigated [14]. In the United States, there is one commercially available topical antidepressant, Zonalon (dextropropoxyphene hydrochloride; Bioglan Pharma, United Kingdom) cream. It is indicated for use by the FDA for the treatment of eczema-associated