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Review Article

MANAGEMENT OF PAIN USING TRANSDERMAL PATCHES - A REVIEW

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ABSTRACT

Transdermal delivery is a non-invasive route of drug administration through the skin surface that can deliver the drug at a predetermined rate across the dermis to achieve a local or systemic effect. It is potentially used as an alternative to oral route of drugs and hypodermic injections. Analgesics are mostly used for various diseases as most of them are associated with severe or mild pain. The use of analgesics as a pain relief patch is now being used commonly. A transdermal analgesic or pain relief patch is a medicated adhesive patch used to relieve minor to severe pain. Currently, the patches are available for many opioids, non-opioids analgesics. local anesthetics, and antianginal drugs. The drugs include fentanyl, buprenorphine ketoprofen, diclofenacepolamine, piroxicam, capsaicin, nitroglycerine, and lignocaine. They are available as both matrix and reservoir patches. This review explores the various drugs used to manage pain and their route of administration in terms of frequency, complications, and effects.

Keywords: Pain, Transdermal drugs, Transdermal patches, Safety.

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INTRODUCTION

Transdermal drug delivery system, now often known as patches, is a non-invasive way of delivering medications across the dermis or skin surface. It is potentially used as an alternative to administer oral route of drugs and hypodermic injections. This drug delivery system can deliver an analgesic at a predetermined rate across the skin to receive a systemic or a local effect.

Transdermal patches are not a new concept. It was first used for systemic delivery, a three day patch, scopolamine to treat motion sickness, approved in the United States in 1979. A decade later, the success of nicotine patches brought in more awareness and usage of transdermal drugs [1].

Today, over 35 drugs are used as transdermal patches, with at least 13 approved molecules. The therapeutic horizon of transdermal patches is now expanding to include hormone replacement, analgesic, relief of chest pain by heart disorders, smoking cessation, and neurologic disorders.

Transdermal patches have a number advantages over oral and hypodermic injections. It provides better biocompatibility in the first pass hepatic metabolism. Increased flexibility in drug administration by patch removal, painless application, and prolonged application for 1 week are other advantages.

However, this drug delivery system has not completely achieved its potential due to few limitations. Local irritation and sensitization of the skin may limit the number of drugs. Successful transdermal drugs have molecular masses that are only up to a few hundred Daltons, thereby limiting the dosage of the drug too. Difficulties in delivering hydrophilic drugs, expense of medication, and delayed absorption are other disadvantages [2].

Transdermal drugs will continue to gain popularity along with further improvements to improve safety and efficacy. A further major step forward will be the production of patches delivering peptide and even protein substances including insulin, growth hormone, and vaccines [4].

Transdermal patches can be categorized into three categories - first generation, second generation, and third generation.

First generation transdermal patches

They are the first set of patches and have been used much in clinics. The transdermal patch design consists of the drug in a reservoir that is enclosed on one side with impermeable backing and adhesive, which contacts the skin [4]. However, due to certain limitations, not all drugs with suitable properties can be delivered. The first generation transdermal patches are limited primarily to the skin barrier that is stratum corneum. Hence, the drugs should be of low molecular weight, lipophilic, and efficient at low doses.

Second generation transdermal patches

Advances in patches to increase the skin permeability, reduce damage to the deeper tissues, and provide better transport into the skin. Certain modifications such as chemical enhancers, non-cavitation ultrasound, and iontophoresis have disturbed the balance in the approach to increase the delivery and also protect the deeper tissues at the deeper level.

Chemical enhancers - they disrupt the highly ordered bilayer of the stratum corneum by inserting amphiphilic molecules to help in better permeation. This, however, can produce skin irritation.

Iontophoresis - they involve administration of drugs into the stratum corneum under low voltage current. They do not disturb the skin barrier, so they can be used for small molecules that carry a charge and some macromolecules up to a few Daltons. Rate of drug delivery can be controlled using a microprocessor.

Non-cavitation ultrasound - physical therapists discovered that massaging anti-inflammatory agents into the skin using ultrasound can increase the efficacy as a skin permeation enhancer [5]. The effects of ultrasound have been limited to small lipophilic molecules. It has been limited due to its associated tissue heating, which can damage the deeper tissue.

Third generation transdermal patches

It involves further advances to improve the skin penetration of drugs and also protection of deeper tissues. Microneedles, thermal ablation, and micro derma abrasion have been experimented in human clinical trials to deliver the macromolecules, therapeutic proteins, and vaccines.

FACTORS INVOLVING TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery depends on a variety of factors such as the size of molecule (<500 Da), pH of drug, state of the skin hydration, stability of the formulation, and lipid solubility.

The energy for drug release is derived from the concentration gradient existing from the saturated solution of drug in the system and the much lower concentration in the skin; drug movement occurs by diffusion [6].

ADVANTAGES OF TRANSDERMAL PATCHES

They are preferred over oral route of drug administration to the systemic circulation for several good reasons;

The bioavailability is increased and improved.

Patients have difficulty in swallowing tablets and capsules, and some patients are tempted to crush tablets to assist in swallowing which destroys any controlled release characteristics of the tablets.

They are preferred over hypodermic injections, which are more painful, generate medical waste, and pose a risk of disease transmission [7].

Improved patient compliance as the treatment is non-invasive, simple, and convenient, and there is greater flexibility in termination of drugs by the removal of patches.

Controlled delivery of drugs through the skin can provide less fluctuation and reduce the drug spike concentration observed after the orally delivered drugs [8].

DISADVANTAGES OF TRANSDERMAL PATCHES

With the advantages, comes along a few set of limitations which makes it inconvenient and unreliable in certain situations.

AGE - It does not a play major role in the delivery of drugs. However, in the case of young infants, it can be difficult to ensure long lasting and adequate adhesion. They are more preferred for the elderly where skin irritation can be less expected, and the reliability is increased. Sites of application - there are variations in penetration according to the site of application. For example, the skin on the palms, face, and genital are more easily permeated, but the skin in the trunk region on the other hand is less easily permeated.

The drug is more effective when it is in occlusive contact with the skin. The main reason for this is increased subcutaneous hydration due to the normal block to evaporation of transepidermal water at the skin surface [9].

Moreover, only limited amount of drugs can be delivered using this method (up to a few 100 Daltons). Furthermore, it has been difficult to deliver hydrophilic drugs.

TRANSDERMAL PATCHES FOR PAIN MANAGEMENT

Transdermal patches are now are used in pain management for both acute and chronic pain.

They are available in various forms which include non-steroidal anti-inflammatory drug patches (NSAID), opioid patches, local anesthetic patches, capsaicin, and nitroglycerine. They are commonly used in pediatric practice.

NSAID patches

NSAIDs are popular drugs, which are used to treat both chronic and acute musculoskeletal conditions [10]. They have the advantage of local action without developing central adverse effects and cognitive defects. Different commercially available NSAID patches are ketoprofen, diclofenac, flurbiprofen, and piroxicam patches [11]. The goal of topical NSAIDs is to minimize systemic adverse effects and encourage compliance. A systematic review of topical NSAIDs for acute musculoskeletal conditions (such as strains and overuse-type injuries) studied 3455 subjects and concluded that the preparations can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs [12].

The most common NSAID patch used is 1% diclofenacepolamine, licensed to treat acute pain in epicondylitis and ankle sprains. A recent review supports that it is being used to help in topical and systemic effect [13]. A reduction in pain scores was demonstrated after 3 hrs in patients with ankle sprains. As diclofenac first appears in the plasma at a mean of 4.5 hrs, after topical application, it is thought that the patch must provide analgesia via a local action. After patch removal, due to a local reservoir effect, the plasma diclofenac half-life is ~9–12 h, compared with 1-2 hrs after oral intake. Systemic transfer after removal of the patch compared with oral forms of diclofenac is only about 2%, so systemic side effects are very rare.

Ketoprofen is another leading NSAID which is available in both patch and gel. Besides COX inhibition, it helps stabilize lysosomal membrane and antagonizes bradykinin action. Patients with rheumatic diseases or trauma reported a better pain relief and functional gain superior to placebo. There is better tolerance, side effects were related to the patch only and cutaneous, not related to the active component [14].

Piroxicam is a NSAID with good analgesic and antipyretic effects. It is utilized for treatment of musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, in soft-tissue disorders, in acute gout, and in post-operative pain [15]. It has high solubility and permeation enhancing properties.

OPIOID patches

Opioid analgesics are prescribed for moderate to severe pain, specially of visceral origin. They are recommended during both non-cancerous conditions, unless when prescribed by the doctor. The opioid patch is a drug reservoir separated from the skin by a membrane. The drug is released over a period.

The fentanyl patches and buprenorphine patches are common opioid patches with high lipid solubility and low molecular weight making them to pass through the dermis more easily.

Fentanyl patches

Fentanyl is a high potency short acting narcotic analgesic, which is widely used as surgical anesthetic and for the control of chronic pain in the form of transdermal patch. They are also used in the palliation of the malignant pain. Because of its low molecular weight and highly lipophilic nature, it is able to penetrate the skin and distribute across different regions of the body. Each patch is designed to maintain a constant plasma fentanyl concentration over a 72 hrs application with maximum plasma concentrations between 12 and 24 hrs. Blood flow and anatomical site of application do not affect the rate of drug delivery. Exposure to a heat source or an increase in body temperature can increase fentanyl delivery by up to one-third. Fentanyl patches are commercially available as 12 μg/hrs, 25 μg/hrs, 50 μg/hrs, 75 μg/hrs, and 100 μg/hrs under the name duragesic/durogesic.

These patches improve pain control and quality of life in patients with chronic pain related to osteo or rheumatoid arthritis [16]. They are useful when oral morphine cannot be taken due to severe renal impairment or when the oral route cannot be used due to vomiting or difficulty in swallowing [17]. Certain studies, also suggest that fentanyl patches, are considered more effective compared to oral morphine in the management of cancer.

Fentanyl patches should not be used in opioid - naïve patients with non-cancer pain because of the potential for serious adverse effects. Fentanyl patches have a delayed onset and a prolonged duration

of action and henceforth, side effects may be difficult to control. Respiratory depression is the most serious opioid side effect associated with fentanyl [18]. Other side effects include vomiting, nausea, and skin irritation due to patch adhesive. Fentanyl causes less constipation when compared to oral morphine [19].

Buprenorphine

Buprenorphine is a strong opioid derived from thebaine, which is of low molecular weight and lipophilic. It is of special interest because of its long period of action, antihyperalgesic effects, and free renal involvement. They were found to be more effective in both chronic and non-cancer patients. It provides good efficacy and tolerability in chronic pain management, providing analgesia for osteoarthritis, low back pain, and other persistent pain syndromes [20]. Clinical trials indicate greater pain relief, improvement of sleep quality, and decreased need for rescue therapy when buprenorphine is used for cancer pain [21]. It is normally started on a small dosage and gradually increasing it after 3 days. It is available in three dosage strengths: 32, 52.5, and 70 µg/hrs over a 72 hrs period. The patch is applied at the upper back, subclavicular region, or chest [14]. Two forms of the patch are available: The 96 hrs Transtec® patch and the 7 day Butrans® patch, both use a matrix design.

Studies showed increased patient compliance for 6 to 12 months but later side effects such as vomiting, nausea, and constipation with use of patch is observed. It produces a ceiling side effect for respiratory depression, especially when combined with CNS depressants [22].

Recently, clinical trials show better characteristics which include free renal impairment and respiratory depression when compared to other opioids such as fentanyl, hydromorphone, methadone, and fentanyl.

Local anesthetic patches

Topical anesthetics have been developed to counteract the discomfort and pain during venipuncture and intravenous catheter insertion. It has fewer side effects and is easy to apply. For proper utility in practice, it should it have a direct local action with limited systemic effect. Transdermal technologies promote the flow of several sizes of various molecules that move through the skin barrier, via the transient microchannels which help provide greater anesthesia in <20 minutes [23]. It has better tolerance with side effects on the cutaneous area.

Most commonly lidocaine patch/versatis patch is used to help in postherpetic neuralgia. Lidocaine is available in 5% patches and is approved for postherpetic neuralgia treatment and other focal neuropathic syndromes, in which other treatments such as, tricyclic antidepressants, and opioids fail. They help in providing beneficial effects on pain, allodynia, quality of life and sleep, with minimal adverse effects. Versatis has dual mode of action, lignocaine diffusion, and the mechanical action of the hydrogel which protects the hypersensitive area. Small randomized controlled trials have confirmed that versatis produced superior pain relief than placebo in short-term studies [24].

Systemic adverse reactions following the appropriate use of the plaster are unlikely since the systemic concentration of lidocaine is very low. Side effects include skin lesion, dizziness vomiting, and hypersensitivity [25].

Capsaicin

They are derived from hot chili peppers from the genus capsaicin and have been used in medical practice. It was first used to treat burning or itching extremities. Later, it was commercially available to treat other disorders such as neuropathic and nociceptive musculoskeletal pain, osteoarthritis, psoriasis, and even migraines [26]. It is available in 8% dermal patch, and it contains 179 g of capsaicin. It is extremely lipophilic and gets easily absorbed into the epidermal and dermal layers. This patch is also known as NGX 4010. Studies show effective results up to 12 weeks after the application of the patch, especially for postherpetic neuralgia [27].

Major side effects include burning sensation, stinging, erythema, and edema and can also correspond with progressive neuronal defunctionalization. Transient hypertension with local pain has also been noted [28]. Capsaicin should not be used in open wounds. In spite of the long-term efficacy, the use of this patch is now limited, due to the side effects which are inconvenient for most of the subjects.

Nitroglycerine

Nitroglycerine is an organic nitrate which acts as a potent analgesic and anti-inflammatory agent. It was traditionally used to treat coronary heart disease, due to its action several cellular systems and central nervous system. However, the effect on coronary artery dilation was modest and did not show much improvement [29]. It is available in the market as Nitro-Dur and Transderm-Nitro®. The absorption is progressive, with the plasma levels constant throughout the day. The effect commences around 30 minutes and lasts up to 6 hrs. Nitroglycerine was also found to be effective in treating rotator cuff lesions and varicose vein sclerosis. They reduce the acute pain when compared to placebo.

Side effects include a headache, palpitations, allergic reactions, contact dermatitis, and flushing. Abrupt suspension of nitroglycerine can also result in acute myocardial infarction and peripheral ischemia [29].

They are recommended to treat local pain, especially in patients contraindicated for NSAID use, as they are free from renal, gastrointestinal, and hematological adverse effects [30].

CONCLUSION

Transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs; the pain and inconvenience of injections. The successes of first generation transdermal patches, second generation chemical enhancers, and iontophoresis are expanding delivery capabilities for small molecules, whereas third generation physical enhancers could enable transdermal delivery of macromolecules and vaccines.

A further major step forward will be production of total dissolved solids units delivering peptide and even protein substances including insulin and growth hormone.

The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase.

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