1. The diclofenac patch is approved for acute pain. How would you define the duration of acute (short-term)?

According to the American Pain Society’s Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, acute pain follows injury to the body and generally disappears when the injury heals.1 This publication does not define the duration of acute pain, and among other organizations there is no “official” definition of acute or chronic pain. Most experts consider pain to become chronic if it continues for more than a few weeks or months after the time that an injury is expected to heal—for example, after approximately 8 to 12 weeks, depending on the source of this information.

The pivotal clinical trials demonstrating efficacy of the diclofenac patch for acute pain were 7- and 14-days in duration.2 Physicians should use the lowest effective dose for the shortest time period consistent with individual patient treatment goals.2

2. Can you comment on the black box warning that appears on the product label of both topical diclofenac preparations?

In 2005, the US Food and Drug Administration (FDA) required the addition of a black box warning to the product label of all cyclooxygenase-2 (COX-2) selective and nonselective nonsteroidal anti-inflammatory drug (NSAID) products, regardless of their method of administration and level of systemic absorption.3 This warning highlights the potential increased risk of adverse cardiovascular (CV) events, in addition to the well-described NSAID class risk of serious, and sometimes life-threatening, gastrointestinal (GI) bleeding. The warnings will not likely be removed from the label of topical NSAID preparations until extensive, long-term, postmarketing safety information has been collected in the United States. However, serious GI or CV side effects have not been identified during the 20 years of European experience with topical NSAIDs, and it is reasonable to explain to patients that there is very little systemic absorption of topical diclofenac compared to oral preparations.

The black box warning provides physicians an opportunity to educate patients on the need to not exceed recommended doses or duration of treatment of any NSAID product, whether prescription or over-the-counter (OTC), as well as contraindications, risk factors, and warning signs of adverse events. Indeed, manufacturers of OTC NSAIDs have also been asked to revise their labeling to provide more specific information about the potential CV and GI risks of their individual products and remind patients of the limited dose and duration of treatment.4
3. Can patients cut the diclofenac patch to use on smaller areas (or to save money) or trim the edges to assist with adhesion to moving joints?

The diclofenac patch product label does not address cutting, so dividing the patch into halves, quarters, or any other size manipulation constitutes off-label use. The patch was designed to deliver a defined concentration of drug to a specific surface area of skin, and cutting the patch will reduce the amount of diclofenac delivered to the area of application. In the absence of clinical data or clinical experience, altering the size of the patch will affect the pharmacology and is not consistent with clinical studies. However, the product label for the Lidoderm® (lidocaine) patch, which is manufactured by the same factory as the diclofenac patch and is similar in design, does advise patients that they may cut it into smaller sizes prior to removal of the release liner—it may be that future studies or clinical experience will demonstrate that this will also be the case with the diclofenac patch. Trimmed into smaller sizes, patches may help with adhesion, but again, doing so constitutes off-label use, and there is currently no data regarding the risks or benefits. The diclofenac patch product label does advise patients that if the patch begins to peel off, the edges may be taped down.

4. My patients are asking if they can use more than 1 patch at a time because they have pain in more than 1 area—for example, for both neck and knee pain. What should I tell them?

Using 2 patches simultaneously will double the amount of medication that is delivered; but the systemic absorption is low at 0.7% of that achieved with oral diclofenac, and so safety problems would not be anticipated at double this level. However, this is not in the product label, which instructs patients to put on 1 patch and change it every 12 hours, or in clinical trials where patients were limited to on-label amounts. Therefore, it is not known what the systemic or local effects would be until further studies are performed or following postmarketing reports to the FDA. It is important for patients to understand that with each additional patch used simultaneously, the systemic absorption rate increases by at least 0.7%, and that safety of this has not been determined.

5. Can patients keep the patch on for longer than 12 hours?

The product label instructs patients to change the patch every 12 hours, which is how the diclofenac patch was studied. It is likely that the effectiveness would decline after 12 hours, although drug does remain in the patch (as much as 170 mg). Changing the patch every 12 hours would be a safer option.
hours also provides patients with an opportunity to regularly check the integrity of the skin and make sure there are no adverse reactions, particularly when initiating treatment.

6. Can patients use a topical NSAID preparation (gel or patch) concomitantly with an oral NSAID, and if so, acutely or chronically?

Currently there are no studies to indicate the risks or benefits of utilizing both topical and oral NSAIDs together. The product label for the diclofenac gel explains that concomitant use of oral NSAIDs has not been evaluated, and may increase adverse effects. The diclofenac patch product label does not address concomitant use of oral NSAIDs, possibly because it is indicated for acute pain, while the diclofenac gel is indicated for chronic osteoarthritis pain, and so might lead to increased systemic exposure over time. Until more data becomes available, physicians should use caution and make sure patients understand the risks of drug-drug interactions, including those associated with OTC NSAIDs.

7. Would you use topical NSAIDs to treat the pain of rheumatoid arthritis?

Topical NSAIDs are only expected to be effective for localized pain problems. The pain of rheumatoid arthritis, which usually involves multiple joints and has a systemic component, would likely not respond to the low systemic NSAID levels that result from topical use (<1% of oral systemic levels). Similarly, the nonlocalized, more generalized joint pain that can occur secondary to chemotherapy in cancer patients is not likely to be amenable to topical NSAID therapy.

8. Do you foresee any problems using the topical NSAID patch or gel in obese patients?

It is not known whether there will be penetration issues in obese patients, but there is certainly much inter- and intra-individual variation in penetration and concentration of topical diclofenac, and obesity may prove to be a factor. It may be more important depending on the area of the body affected and an individual’s pattern of fat distribution—for example, the knees, elbows, and ankles do not tend to accumulate as much fat as the thighs or buttocks. The product labels for the diclofenac patch and gel do not address this.

9. Does topical diclofenac interfere with the antiplatelet effect of low-dose aspirin, potentially rendering aspirin less effective when used for cardioprotection and stroke prevention?
Aspirin reduces the risk of myocardial infarction and stroke by irreversibly acetyling a serine residue in platelet cyclooxygenase, the predominant product of which in platelets is thromboxane. Once cyclooxygenase has been acetylated by aspirin, the substrate’s access to its active site is impeded for the lifetime of the platelet. Thus, the formation of thromboxane requires the synthesis of new platelets, which are regenerated at a daily rate of approximately 10%.

Patients with CV disease who receive low-dose aspirin often have a pain problem for which they receive an NSAID. NSAIDs, unlike aspirin, bind reversibly at the active site of cyclooxygenase, usually depressing platelet thromboxane formation for only a portion of the dosing interval. Investigators who studied potential competitive interactions between a low-dose enteric-coated aspirin administered once daily and commonly prescribed NSAIDs found that the effects of an aspirin regimen commonly used for cardioprotection would be negatively influenced by ibuprofen. Serum thromboxane formation and platelet aggregation by aspirin was blocked when a single daily dose of ibuprofen was given before aspirin, as well as when multiple daily doses were given. In contrast, the concomitant administration of oral diclofenac, rofecoxib, and acetaminophen did not affect the pharmacodynamics or limit the cardioprotective effects of aspirin. Other investigators have also found support for the hypothesis that ibuprofen may diminish the cardioprotective effects of aspirin.

The FDA warns that published and unpublished human ex vivo studies have demonstrated that ibuprofen interferes with the antiplatelet activity of low-dose aspirin (81 mg) when they are ingested concurrently. Thus, treatment with oral ibuprofen, but not oral diclofenac, in patients with increased CV risk may limit the cardioprotective effects of daily low-dose aspirin. Therefore, topical diclofenac, which has 100 times less systemic absorption than oral formulations, would appear to pose no problems.

10. The meta-analyses of clinical studies seem to show that topical NSAIDs are not very efficacious, with high placebo response rates and a number needed to treat (NNT) of 3.8 and 4.6 for acute and chronic pain, respectively. Please comment.

No analgesic will be effective in 100% of patients or completely eliminate pain, and placebo effect and spontaneous remission of acute injuries can blur the line of effectiveness. However, these meta-analyses showed response rates of 57%, which is similar to the 62% rate for oral NSAIDs in acute pain, and 37% for both topical and oral NSAIDs in chronic pain. Postmarketing studies and clinical experience with topical agents will be needed to determine whether this similar efficacy will come with fewer adverse effects compared with oral NSAIDs. Pharmacoeconomic and return-to-work data are also needed, but enabling some people to achieve improved functioning—even 24 hours earlier—is clinically significant.
Particularly for chronic pain, it is important to use topical agents as just one part of the treatment plan, which might include physical therapy, exercise, and other nonpharmacologic/rehabilitative therapies.

References


