Low dose transdermal administration of buprenorphine with a seven days patch for pain that is not relieved sufficiently by nonopioid analgesics

Harald Breivik MD, DMedSci, FRCA Professor
University of Oslo
Department of Pain Management and Pain Research, Oslo University Hospital, Oslo, Norway

Paliat. med. liec. boles., 2011, 4(2): 55–56

According to the World Health Organization (WHO) osteoarthritis (OA) is one of the ten most disabling disease in the developed countries, a painful condition that is increasing as a health care problem as the elderly population increases in numbers (1). When possible, surgical replacement of a painful weight bearing joint relieves pain and improves quality of life. Guidelines for nonsurgical management of OA-pain in the elderly no longer recommends NSAIDs or COX-2-specific inhibitors because of the many serious adverse side-effects of these drugs in the elderly, e.g. renal failure, increased blood pressure, myocardial infarction, bleeding gastrointestinal ulcers: Therefore NSAIDs and COX-2-specific inhibitors should be used only occasionally and only for a few days when severe flare-ups of pain occur (2, 3).

The choices available for pharmacological pain relief in the elderly is further restricted by concerns about increased risks of falls, fractures, myocardial infarctions, and even increased all-cause mortality among elderly patients taking potent opioids (4).

There are components of neuropathic pain mechanisms in OA (5) and therefore adjuvant analgesics like gabapentin, pregabalin, and nortriptyline, may offer some relief (6). However, these drugs may, like opioids, increase daytime sedation and dizziness, increasing the risk of falling. Especially amitriptyline should not be used in ambulatory elderly patients for these reasons.

Opioid analgesics, especially during initiation of treatment and when doses are escalated, cause dose-related sedation, dizziness, cognitive impairment, nausea, vomiting, and constipation. Bolus doses of opioids may be more likely to precipitate dizziness and nausea, whereas there are less such side effects when opioids are administered at a steady, low rate.

Patients with advanced OA have pain most of the time, also during the night, reducing quality and duration of restful sleep. Paracetamol is now the only non-opioid analgesic drug (outside countries where metamizol is still available) that can be recommended as a first choice analgesic in elderly patients. Paracetamol should be used in doses up to 4 grams per day, liver enzymes being monitored.

However, paracetamol is often not sufficiently potent for OA-pain. Buprenorphine can now be delivered in low doses at steady rates through the skin as the 7-day transdermal buprenorphine patch (Norspan®). This may be an option for treating OA-patients who need a more potent analgesic than paracetamol.

The buprenorphine patch (Norspan®) with median dose 10 µg/hour was studied in a double blind, randomized, placebo-controlled study for OA-pain in opioid naïve patients (7). This study documented that it is possible to maintain blinding for up to half a year between an opioid and placebo. The study also reconfirmed the well documented, but not generally acknowledged phenomenon that in prolonged studies where blinding is well controlled and a team of investigators keep good and close contact with the patients, a significant non-specific „context-sensitive-therapeutic-effect" develops. Therefore, pain intensity decreased steadily in both groups throughout the half year the study lasted. However, daytime movement-related pain decreased significantly more ($P < 0.03$) in the buprenorphine group compared with the placebo group. There were more nausea in the buprenorphine group in the first few days, and more patients discontinued before the end of the 6 months double blind period due to such opioid side effects compared with the placebo group. Still, at the end of the double blind period the patients' global impressions of improvement were significantly ($P < 0.02$) superior after buprenorphine than after placebo treatment.

Therefore, OA-patients, who really need an opioid in addition to oral paracetamol (and possibly a topical NSAID?) a regimen to consider is to give the patient the benefit of a very low, constant administration of buprenorphine with the 7-day transdermal delivery system, starting with only 5 µg/hour. If there is a flare-up of pain, in spite of ongoing low-dose buprenorphine patch treatment, I would offer extra doses of paracetamol – up to 4 g per 24 hours, add a single dose of ibuprofen 400 mg times two or diclofenac 75 mg once daily for 1 – 2 days.

If this regimen still leaves the patient in severe pain, and only provided the patient has adequate monitoring by relatives and/or a nurse or nurse's assistant, would I add a fast onset, moderate duration opioid, e.g. an oxycodone 5 – 10 mg immediate release tablet. This dose may be sufficient as an add-on to buprenorphine 5 – 20 µg/hour because there are definite additive analgesic effects between buprenorphine and traditional µ-opioid agonists (8). Small doses of opioids „as needed" reduces total dose and burden of opioid adverse effects, compared with time-contingent opioid dosing for chronic noncancer pain (9).

All available non-pharmacological means of reducing suffering in patients with chronic pain must be exploited as well. In the Nordic countries, lack of sunshine and therefore lack of vitamin D needs more awareness (10). Lack of vitamin D during the dark months of winter tends to increase suffering from chronic pain which is more prevalent in Iceland and Norway than in Spain (11, 12).

Acknowledgement
This paper is base don an article in PainEurope, 2011: Breivik H. Avoiding the Scylla of NSAIDs and the Charybdis of high dose opioids for osteoarthritis pain: Low-dose transdermal buprenorphine is an appropriate choice when analgesics are needed for severe osteoarthritis pain in elderly patients. PainEurope 2011.

References

1. <http://www.who.int/chp/topics/rheumatic/en>. Last accessed February 28, 2011.
2. American Geriatric Society (AGS) Panel on pharamcological management of persistent pain in older persons. J Amer Geriatc Soc 2009; 67: 1331–1346.
3. 2008 European Guidelines for primary care management of chronic osteoarthritis pain. [on-line]. Last accessed February 28, 2011. <http://eGuidelines.co.uk>.
4. Graf J. Analgesic use in the elderly. Archi Intern Med 2010; 170: 1976–8.
5. Kidd BL. The mechanisms of chronic pain. In: Breivik H, Shipley M (editors). Pain best practice and research compendium. London: Elsevier 2007: 17–26.
6. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132: 237–251.
7. Breivik H, Ljosaa TM, Stengaard-Pedersen K et al. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. Scand J Pain 2010; 1: 122–41.
8. Kress HG. Clinical update on the pharmacology, efficacy and safethy of transdermal buprenorphine. Eur J Pain 2009; 13: 219–230.
9. Von Korff M, Merrill JO, Rutter CM, Sullivan M, Campbell CI, Weisner C. Time-scheduled vs pain-contingent opioid dosing in chronic opioid therapy. Pain 2011 Feb 4. [Epub ahead of print].
10. Breivik H. Whether the weather influences pain: High prevalence of chronic pain in Iceland and Norway: Common genes? Or lack of sunshine and vitamin D? Scand J Pain 2010; 1: 149–150.
11. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European Journal of Pain 2006; 10: 287–333.
12. Gunnarsdottir S, Sandra WE, Serlin RC. A population based study of the prevalence of pain in Iceland. Scand J Pain 2010; 1: 151–7.

Harald Breivik MD, DMedSci, FRCA Professor
University of Oslo
Department of Pain Management and Pain Research, Oslo University Hospital
Oslo, Norway
harald.breivik@medisin.uio.no

Opioidové analgetiká v náplasťovej forme – poznámka k situácii v SR

Krátka zmienka prof. Breivika z Osla o príchode 7 dní účinkujúcej buprenorfínovej náplaste (Norspan) na nórsky, resp. škandinávsky trh je potešujúcou správou. Náplasťové formy silných opioidových agonistov sa v indikácii chronická bolesť silnej intenzity nádorového aj nenádorového pôvodu javia u väčšiny pacientov ako ideálna lieková forma. Je to predovšetkým pre zabezpečenie kontinuálnej hladiny účinnej látky v plazme doteraz až na 72 hodín, čo prináša nielen stabilné tíšenie bazálnej bolesti, ale aj znížený výskyt nežiaducich účinkov tejto liečby, a to predovšetkým nauzey, malátnosti a obstipácie. Vďaka užívaniu pomaly sa uvoľňujúcich opioidových analgetík sa mohla významne zredukovať potreba dlhodobého užívania relatívne nebezpečnejších nesteroidových antiflogistík.

Príchod známeho opioidového analgetika v overenej aplikačnej forme, ale s významne predĺženou dobou uvoľňovania účinnej látky z 3 na 7 dní, iste prinesie vybraným trpiacim pacientom ďalšie skvalitnenie úľavy od silnej bolesti. Nám na Slovensku ostáva už len čakať na jeho registráciu na našom trhu.

doc. MUDr. Igor Martuliak, PhD.
Algeziologická klinika SZU FNsP F. D. Roosevelta
Nám. K. Svobodu 1, 975 17 Banská Bystrica
imartuliak@nspbb.sk

*Časopis **Paliatívna medicína a liečba bolesti** vychádza v spolupráci so Slovenskou spoločnosťou pre štúdium a liečbu bolesti (**www.pain.sk**) a s Českou spoločnosťou paliatívnej medicíny (**www.paliativnimedicina.cz**).*