Acta Anaesthesiologica Taiwanica 53 (2015) 71–76

Contents lists available at ScienceDirect

Acta Anaesthesiologica Taiwanica

journal homepage: www.e-aat.com

Original Article

The unique role of transdermal buprenorphine in the global chronic pain epidemic

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ARTICLE INFO

Article history:
Received 10 June 2015
Accepted 11 June 2015

Key words:
access to medicines;
adverse effects;
analgesia;
buprenorphine;
drug abuse;
transdermal patch

ABSTRACT

Pain is a global epidemic, exacerbated by barriers to access of opioid analgesics. Regulations about opioids attempt to protect public health from the risks of harmful use of opioids, diversion, and dependence. Transdermal buprenorphine is an effective opioid analgesic agent with unique properties that may make it particularly well suited for more widespread use. It is a versatile analgesic product with demonstrated safety and effectiveness in cancer and noncancer pain populations. Its pharmacological properties make it a first-line opioid analgesic for geriatric patients and patients with renal dysfunction; no dosing adjustments need to be made. The 7-day transdermal delivery system is convenient for patients and promotes compliance. A low dose of buprenorphine can provide effective and well-tolerated pain relief. Although buprenorphine has been associated with certain opioid-related adverse effects, such as dizziness and nausea, it is associated with a lower rate of constipation than many other opioid analgesics. The potential for nonmedical use of buprenorphine is relatively low compared with other opioid agents. Buprenorphine has a relatively low *likeability* for nonmedical use and the transdermal matrix patch renders the substance particularly difficult to extract for illicit purposes.

1. Introduction

In 1978, Dr Donald R. Jasinski of the US Addiction Research Center described buprenorphine as a substance with a *unique pharmacology with immediately obvious therapeutic applications as an analgesic of low abuse potential*.[1] More than 30 years of subsequent clinical data support this statement. The role of buprenorphine continues to be unique among opioid analgesics, particularly in light of the global chronic pain epidemic.

About two-thirds of the world's population (~4.65 billion people) live in countries where opioid consumption is very low or near to zero, forcing patients with cancer, lethal injury, surgery, human immunodeficiency virus, and chronic pain syndromes to suffer with uncontrolled pain.[2] Pain knows no borders. In Taiwan, for example, a substantial portion of the population suffers from chronic noncancer pain. A survey of community-dwelling senior citizens in Taiwan revealed a pain prevalence of 50.0%.[3] A study conducted in Taipei ($n = 92$) found that 42% of seniors suffered chronic pain.[4] In a survey of 151 geriatric osteoarthritis or rheumatoid arthritis patients in Taiwan, 11% considered themselves disabled.[5] A cross-sectional study of Taiwanese nursing aides ($n = 244$) found the prevalence rate of chronic pain was 8.6%.[6]

Although the World Health Organization (WHO) advocated the use of oral opioid analgesics for moderate to severe cancer pain as early as 1986,[7] the ensuing decades have created formidable barriers to access to these medicines in an effort to protect public health from harmful use of opioids. In September 2014, a group of pain specialists met in Taipei to discuss the potential role of transdermal buprenorphine as an important and unique analgesic

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http://dx.doi.org/10.1016/j.aat.2015.06.001

agent in the global fight against chronic pain, particularly in light of its deregulation in Taiwan.

2. The burden of chronic pain

Adult chronic noncancer pain prevalence in the USA is 30.7% (95% confidence interval, 29.8–31.7%), of whom about one third (32%) rate their pain intensity level as severe.[8] Chronic noncancer pain prevalence increases with age, which means that the prevalence is likely to rise markedly with the aging demographics of many advanced nations in North America, Europe, and Asia. Although there is evidence and guidance in the literature that chronic noncancer pain may be appropriately treated with opioid analgesics,[9–12] concerns have been raised about the longer-term use of opioid therapy for noncancer pain.[13]

Nevertheless, chronic opioid therapy for chronic noncancer pain has been increasing in the USA over the past 2 decades,[14] and strong opioids, such as oxycodone and hydrocodone, are among the most frequently prescribed analgesics there.[15] Ninety percent of American chronic noncancer patients with moderate and severe pain take opioids, most of which are in Schedule III and IV of the US Controlled Substances Act.[16] Compared with this use pattern, opioid consumption in other parts of the world is very low; in many parts of the world, opioids might not even be considered for the control of noncancer pain.[17,18]

Chronic pain patients often have multimechanistic pain (for example, nociceptive pain with an additional neuropathic and/or visceral component).[19] Chronic pain patients may have different types of pain related to comorbid conditions, such as diabetes, or there may be comorbid complications that influence prescribing choices, such as cardiovascular disease or morbid obesity. Therapy should be based not only on the patient's condition, but also on the patient's lifestyle.[20] Clinicians should consider the patient's occupation and physical demands, medical history, current medication regimen, recreational substance regimen, tobacco use, alcohol consumption, and the use of over-the-counter medicines or supplements.

The optimal treatment paradigm for a patient with moderate to severe chronic noncancer pain involves evaluation, assessing his or her risk for potential opioid abuse, obtaining an informed consent and, in some cases, signing a formal treatment agreement, and then commencing therapy.[21] Once the appropriate dose is titrated, the patient should be monitored and risk should be reassessed periodically.[22] If a particular opioid agent is not effective or not well tolerated, another opioid can be tried (opioid rotation). Discontinuation of the medicine should be considered if: (1) opioid therapy is not effective or not well tolerated; (2) the patient wishes to discontinue treatment; or (3) there are signs that the patient is using the medicine in a harmful way. Alternative analgesic solutions should then be considered. In order to prevent withdrawal syndrome, opioid therapy should not be discontinued abruptly, but rather be tapered over time.

3. Transdermal buprenorphine

Buprenorphine is a semisynthetic opioid that has been termed a partial μ-opioid receptor agonist and a partial κ-receptor antagonist.[23,24] Dissociation from the opioid receptors proceeds slowly, resulting in a prolonged duration of action and a relatively prolonged and weak withdrawal. Buprenorphine is available in multiple formulations (oral, sublingual, parenteral); our proceedings focused on the transdermal or patch delivery system. Transdermal formulations have been recognized as an effective, convenient delivery method that encourages patient compliance.[25] Transdermal buprenorphine (marketed under different names depending on the country, including Butrans, Norspan, Restiva, and Sovenor) is available in 7-day patches in three strengths: 5 μg/h, 10 μg/h, or 20 μg/h. Opioid-naïve patients can be initiated on the 5-μg/h patch, and higher-strength patches provide effective pain control in opioid-experienced patients.[26]

Transdermal buprenorphine has demonstrated good overall efficacy and tolerability in clinical studies in patients with chronic noncancer pain, such as musculoskeletal pain associated with osteoarthritis and low back pain, among others.[27] Transdermal buprenorphine is a versatile analgesic that has been shown to offer effective pain relief in a variety of different patient populations and cancer as well as noncancer pain syndromes.[27] A selection of recent clinical trials are outlined in Table 1. A review of randomized clinical trials assessing the use of transdermal buprenorphine versus placebo or a comparator drug for the relief of pain in cancer patients (8 studies identified, $n = 909$), found that the number-needed-to-treat was 5.8.[28]

In addition to providing effective analgesia, transdermal buprenorphine may be beneficial for functional improvement in patients with chronic noncancer pain.[29] The odds ratios for 10 activities of daily living related to sleeping, bending, lifting, working, and so on, reached multiplicity-adjusted statistical significance and indicated that patients in the transdermal buprenorphine group had a greater ability to perform activities of daily living than placebo patients at 12 weeks.[29] Transdermal buprenorphine may also be combined with other agents for multimechanistic pain syndromes.

4. Clinically important attributes of buprenorphine

Buprenorphine may be recommended as a first-line analgesic product for elderly pain patients and/or in pain patients with compromised renal function.[30] Buprenorphine is primarily excreted through the feces and does not accumulate in the body, making it suitable for patients with compromised renal function.[23] These two pain patient subpopulations (the elderly and those with renal impairment) are frequently encountered in clinical practice.[30] The important and unique role of transdermal buprenorphine in these subpopulations is discussed below.

4.1. The elderly

The American Geriatric Society recommends opioids as first-line treatment in geriatric chronic pain patients.[12] This guideline advocates that first-line treatment should be an opioid; nonsteroidal anti-inflammatory drugs are to be reserved for flares or sudden exacerbations of pain, because they have been associated with gastrointestinal and cardiovascular side effects and are not considered appropriate for long-term use in elderly patients, particularly at high doses.[31,32] Prescribing opioid analgesics for the elderly can be challenging, in that metabolism slows in older individuals, such that dosing may need to be reduced and/or dosing intervals prolonged in order to avoid long-term drug accumulation. In addition, elderly patients may have multiple comorbid conditions, including hepatic or renal dysfunction. Buprenorphine does not accumulate in the system and dosing adjustments need not be made for those with slower metabolisms or renal failure.[30] In a study comparing older patients (>65 years) with two younger patient groups (those aged 51–64 years and those aged ≤50 years) treated with transdermal buprenorphine for noncancer pain, buprenorphine was found to provide effective pain relief in all age groups.[33] In fact, the daily mean pain intensities on Days 10–28 of the study were significantly lower in the elderly patients ($p < 0.005$) compared with the two younger groups (35.8% vs. 39.8% and 39.9%, respectively).[33] This level of analgesia, combined with

Table 1
Selection of the recent clinical trials with transdermal buprenorphine in diverse pain patient populations. This list is not exhaustive, but illustrates the various potential applications of transdermal buprenorphine for pain.

Study	Patients	Study design	Drugs	Results	Adverse events	Comments
Cancer pain						
Palliative						
Corli et al 2012[55]	258 palliative cancer patients with moderate to severe pain	Interventional study	Compared oral morphine, oral oxycodone, TDF, and TDB, titrated to individual patient needs	*Full responders* were least frequent in morphine group and morphine patients had to switch opioids more than often than TDB patients (24.4% vs. 8.6%)	Oxycodone, TDF, and TDB were better tolerated than oral morphine	3-week study
Noncancer pain						
Gordon et al 2010[56]	78 chronic low back pain patients	Randomized, double-blind, placebo-controlled, crossover study	TDB 10-μg/h and 20-μg/h patches titrated to patient need vs. placebo	At 8 weeks, TDB was more effective than placebo at relieving pain	TDB patients had significantly higher rates of nausea, dizziness, vomiting, somnolence and dry mouth compared with placebo (but not constipation). No serious AEs were reported in either group.	Improvements in pain scores were sustained throughout a 6-month open-label extension period
James et al 2010[57]	246 OA patients	Randomized, double-blind, parallel group study	Low-dose TDB (5 μg/h, 10 μg/h, or 20 μg/h) versus buprenorphine sublingual tablets (200 μg and 400 μg), then titrated	Both groups had significantly reduced pain intensity, less pain-related sleep disturbance, and improved QOL	Significantly fewer TDB patients had nausea, dizziness, or vomiting compared with sublingual buprenorphine patients	28-day study
Ripa et al 2012[58]	198 OA patients	Randomized double-blind study	Oral hydrocodone and acetaminophen conversion to/from TDB 10 μg/h or 20 μg/h	Analgesic efficacy was similar over 7 d for both products	Severe treatment-related AEs were ≤2% for both groups	Five of the hydrocodone patients in this study were suspected of drug abuse or diversion; no such problems with TDB
Steiner et al 2011[59]	1160 low back pain patients who responded to TDB in an open-label study	Randomized, double-blind study	TDB 5 μg/h or 20 μg/h vs. 40 mg/day oral oxycodone immediate release (active comparator)	Average pain in last 24 h at 4 wk, 8 wk, and 12 wk favored oral oxycodone over TDB but all treatments were effective	AE rates were 59% (TDB 5 μg/h), 77% (TDB 20 μg/h), and 73% (oxycodone)	All patients were opioid-experienced upon entry into study
Geriatric						
Conaghan et al 2011[60]	220 elderly patients (≥60 y) with hip and/or knee OA	Randomized study	TDB (5–25 μg/h) plus oral acetaminophen (1 g 4 times daily) vs. oral codeine-acetaminophen fixed-dose combination products (8/500–30/500 mg tablets 4 times daily)	Both treatments effectively reduced pain but TDB patients used significantly less rescue medication	AEs were similar (86.4% for TDB vs. 81.7% in comparator group)	
Wahle et al 2013[61]	2713 elderly multimorbid patients with chronic noncancer pain	Postmarketing surveillance study, noninterventional	7-d TDB (≥10 μg/h) over 8 wk	Mean pain intensity decreased significantly and quality of sleep, quality of life, social activities, and self-reliance improved significantly	3% had adverse drug reactions; tolerability was good or very good in >90%	
Opioid-naïve patients						
Mitra et al 2013[62]	46 opioid-naïve adults with persistent noncancer pain	Prospective randomized 12-month clinical trial	TDB or TDF, patients titrated individually	Both agents improved pain intensity, sleep, and mood, no differences between groups but a higher equipotent dose of fentanyl was needed for comparable pain relief. Clinical improvement occurred in both groups in first 6 mo but only 11% of TDB and 13% of TDF patients had sustained relief after 6 mo	41% of TDB and 37.5% of TDF patients discontinued the patch because of side effects or lack of efficacy	TDB patients had more local skin reactions than TDF patients. 31% of TDB and 57% of TDF patients needed additional pain medication at 3 mo. TDB patients had significant improvements in depression.
Steiner et al 2011[26]	1024 low back pain patients who responded to TDB in an open-label study	Enriched randomized double-blind placebo-controlled study	TDB 10 μg/h or 20 μg/h vs. placebo	TDB patients had significantly lower pain scores than placebo patients at 12 wk	Treatment-emergent AE rates were 55% for TDB and 52% for placebo patients	All patients were opioid naïve upon entry into study

AE = adverse event; OA = osteoarthritis; NS = not significant; PONV = postoperative nausea and vomiting; QOL = quality of life; TDB = transdermal buprenorphine; TDF = transdermal fentanyl.

the ease of a 7-day dosing regimen, enables an effective treatment option in elderly patients.

4.2. Renal impairment

Renal impairment, which is associated with hypertension and type II diabetes among other conditions, can have therapeutic consequences for the safety of medicines. For that reason, prescribing choices may be limited in patients with kidney dysfunction, because they have an impaired ability to properly metabolize or clear compounds. Physicians prescribing opioids are generally advised to decrease doses and/or extend dosing intervals in patients with compromised renal function.[34] This is not the case with buprenorphine. In contrast to morphine and other opioid agents, the pharmacokinetics of buprenorphine remain unchanged in hemodialysis patients. Thus, buprenorphine may be considered one of the safest opioid analgesics for use in patients in renal failure or on dialysis.[35]

In a study of 15 patients undergoing lower abdominal or peripheral body surface surgery, a single intravenous dose of 0.3 mg of buprenorphine was administered; nine of the patients in this study had dialysis-dependent renal failure while six patients had normal kidney function.[36] Blood was sampled up to 24 hours and no difference in buprenorphine kinetics could be determined between healthy and renally-impaired anesthetized patients: mean elimination half-life was 398 minutes and 239 minutes, respectively; clearance was 651 ml/min and 988 ml/min, respectively, and the apparent volume of distribution at steady state was 313 l and 201 l, respectively.

5. Adverse events associated with transdermal buprenorphine

Some of the adverse effects associated with transdermal buprenorphine are typical of opioid analgesics (dizziness, nausea, vomiting, and so on) with a few important distinctions. There is less constipation with buprenorphine than other opioids because buprenorphine does not appear to affect the sphincter of Oddi.[37] Unlike other opioid agents, buprenorphine has not been associated with hypogonadism, because it does not adversely impact the hypothalamic–pituitary–adrenal axis.[35]

Respiratory depression is an opioid-associated adverse event with potentially life-threatening consequences. Buprenorphine causes limited respiratory depression with a ceiling effect at higher doses compared with fentanyl, which is associated with dose-dependent respiratory depression with apnea.[38,39] This ceiling effect of buprenorphine relating to respiratory depression does not translate to a ceiling effect associated with analgesia.

6. Abuse and dependence potential

The selection of any analgesic product for a given patient involves a balancing of benefits associated with that agent against risks that agent could confer. These risks include the risk that the medicine might be used in a harmful way or diverted; the risk that the patient could become dependent on the substance over time; toxicity concerns associated with overdose; and the risk of respiratory depression.[1] Data from Mundipharma's global safety database demonstrate that the reporting rate of harmful use or diversion of transdermal buprenorphine is approximately one case for every 173,652 patient–months exposure, which compares with the reporting rates for other opioids in Mundipharma's safety database of one case per 18,929 patient–months exposure or one case for every 449,856 patient months for tramadol. Limitations of analyzing data from voluntary reporting systems include under-reporting, various reporting biases (e.g., differences in reporting rates for newly marketed products, biases due to raised awareness for specific events in the media), and incomplete unverified data (e.g., differences in individual interpretation of events).

Sudden discontinuation of opioid medicines may result in withdrawal syndrome. Buprenorphine has withdrawal syndrome rates similar to other opioids, however, its slower-than-usual dissociation from opioid receptors may account for its relatively mild withdrawal symptoms compared with other opioids.[1,40] Buprenorphine withdrawal syndrome is more easily managed clinically than other types of opioid withdrawal.[41]

It is important to properly contextualize the risk of opioid toxicity. From studies in the USA, it has been shown that about 80% of American opioid patients are prescribed low doses (<100 mg of oral morphine equivalent/day) from a single prescriber.[42–44] About 20% of all US opioid overdoses occur in this population. About 10% of the opioid patients in the USA have a high-dose prescription (≥100 morphine equivalents/day) from a single prescriber and this group accounts for about 40% of prescription opioid overdoses.[45,46] The major concern in the USA is the 10% of opioid patients who possess and continue to seek multiple opioid prescriptions from multiple prescribers for high daily doses.[47] This group accounts for about 40% of opioid overdoses and may be responsible for much diversion of medicines.[47] Thus, the *typical pain patient* is not at particularly high risk for opioid overdose or other harmful use of opioids.[48,49] However, there is a small but very active subset of chronic patients likely to misuse opioids.[50]

The potential for harmful use of an opioid agent is defined by its pharmacokinetic properties. In general, people who use opioids prefer substances with a rapid onset of action that reach peak plasma concentration quickly.[51] Substance *likeability* is often used to measure its potential for nonmedical use and reward-reinforcing effects.[52] Opioid products that would be less likeable would be those that had a ceiling effect on substance-induced euphoria, those which achieved systemic exposure only gradually, and those which relied on low peak plasma concentrations for effectiveness—all features that are characteristics of transdermal buprenorphine.

Many people who use opioids nonmedically will tamper with commercial products in order to extract as much opioid as possible, which is then ingested, inhaled (*snorted*), smoked, injected, or taken rectally (*plugged*).[53,54] The active agent must be extracted from the product, which often requires special skills, equipment, and time on the part of the user. Nevertheless, certain people who use substances nonmedically will devote the effort to extract highly attractive substances; this would not often be the case with buprenorphine. Transdermal buprenorphine may have an added advantage in this respect: buprenorphine cannot be extracted from the patch matrix directly with a needle and syringe, and successfully extracting the active agent from the patch matrix in sufficient quantities via other methodologies is complex and time-consuming. In summary, other full agonist opioids are more desirable for nonmedical misuse, and other formulations of opioids are more attractive and less challenging to misuse than the transdermal formulation of buprenorphine.

7. Conclusion

Pain transcends borders. Chronic pain is a global public health concern with a massive and underappreciated impact on global productivity. There are numerous barriers to effective pain control with opioids and many of these barriers must be removed or at least lowered to allow adequate analgesia. Transdermal buprenorphine may be an important analgesic for these reasons: it is effective, well tolerated, and has a relatively low potential for nonmedical use compared with other opioids. It is appropriate for

use in renally impaired patients and the elderly (two important pain subpopulations) and has been shown to confer improvements in quality of life, sleep, function, and mood, as well as pain relief.

Conflicts of interest

J.P. is a consultant, researcher, and speaker for Mundipharma, Purdue Pharma LP, Grunenthal, Janssen, Astra Zeneca, and Baxter Healthcare. W.S. regularly works for the World Health Organization on issues related to controlled substances, including access to opioid analgesics. He received funding from Mundipharma and Grünenthal for speaking on accessibility of analgesia at conferences and meetings. K.S., J.L.S., and J.C.W. are employees of Mundipharma Research Ltd. J.H. provides consulting services through Pinney Associates on drug dependence potential assessment and regulation and this has included speaking on accessibility of analgesia at conferences and meetings funded by Mundipharma.

Acknowledgments

The authors acknowledge and express their appreciation for medical writing assistance from Jo Ann LeQuang of LeQ Medical, Angleton, TX, USA, to prepare this manuscript based on the authors' presentations at the Controlled Drug Forum in Taipei, September 26th, 2014 and the 58th Annual Meeting and Scientific Conference of the Taiwan Society of Anesthesiologists in Taichun, September 27th, 2014.

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