

Transdermal buprenorphine in the management of persistent pain – safety aspects

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Abstract: By virtue of their efficacy, opioid analgesics have long been used for the treatment of both acute and chronic pain. Concerns regarding their safety and tolerability have frequently prevented this class of drugs achieving their full therapeutic potential, and their reported association with drug abuse and dependence has led to a reduced acceptance by many patients. Indeed, there is a variety of opioid-like side effects which are common to all members of the class, but some opioids have a more favourable safety profile than others. Buprenorphine is a semisynthetic opioid with a μ -agonistic and κ -antagonistic receptor-binding profile. Studies over the past two decades have shown buprenorphine to have a complex and unique pharmacological profile, which results in enhanced therapeutic benefits combined with a favourable safety profile. Having been underused before, the development of a new transdermal drug delivery system for buprenorphine has revived interest in this substance. Transdermal buprenorphine (Gruenthal GmbH, Aachen, Germany) provides a noninvasive method of rate-controlled drug release ensuring constant and predictable serum buprenorphine levels over a prolonged period. This preparation has been shown to be advantageous for long-term treatment of chronic pain patients providing reliable pain control, few adverse events, and good patient acceptance.

Keywords: opioids, chronic pain, buprenorphine, transdermal buprenorphine, safety

Introduction

Opioid analgesics play an important role in the management of acute and chronic pain of both cancer and non-cancer origin, particularly where non-opioid analgesics have proven to be not effective. The World Health Organisation (WHO) guidelines for cancer pain management propose the use of an analgesic pain ladder, suggesting the use of mild opioids such as codeine for mild to moderate pain (step II) progressing to the use of strong opioids such as morphine to control severe pain (step III) (WHO 1996).

Despite their proven efficacy for the control of chronic pain, the use of opioids have frequently been curtailed due to concerns regarding safety and tolerability. By its very nature, persistent pain necessitates the use of long-term therapy, which in the case of opioids leads to mostly unsubstantiated fears concerning drug abuse, addiction, and dependency. For many patients with chronic pain, however, opioid therapy may be the only effective treatment. Side effects and safety are of paramount importance in these cases where quality of life is often compromised. A number of treatment goals have now been proposed for improved patient therapy, most of which are based on the WHO recommendations. These include providing a stable plasma drug concentration to ensure long lasting and effective pain relief, formulations that provide a long duration of action, noninvasive administration, and an improved quality of life.

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Buprenorphine, a potent opioid analgesic, has been available in parenteral and sublingual formulations for more than two decades. It offers a number of advantages when compared with morphine and its physicochemical properties make it a suitable candidate for administration in a transdermal preparation.

In this paper we will review the safety aspects of long-term opioid therapy and show why and how transdermal buprenorphine is especially suitable for chronic pain management.

Buprenorphine

Physicochemical properties

Buprenorphine is a semi-synthetic derivative of thebaine, one of the chemically most reactive morphine alkaloids. Buprenorphine has a molecular weight of 467 and its structure is typically opioid with the inclusion of a C-7 side-chain containing a t-butyl group. This group confers overall lipophilicity on the molecule which has an important influence on its pharmacology.

Opioids exert their pharmacological effects by binding to opioid receptors. The pharmacological effects are determined by the nature of opioid-receptor interaction. Some of these effects such as analgesia, mediated by an agonistic action at the μ -opioid receptor are desirable, whereas others such as nausea, sedation, or constipation can be considered as unwanted adverse effects. Buprenorphine is a μ -opioid receptor agonist with high affinity, but low intrinsic activity. Compared with morphine which behaves as a full μ -opioid agonist, buprenorphine is usually defined as a partial μ -opioid agonist that shows high affinity for and slow dissociation from the μ -opioid receptor. A full dose-dependent effect on analgesia has been seen within the clinically relevant dose range (up to 10 mg), but no respiratory depression which levels off at higher doses (Dahan et al 2005). Clinically, there is also a less marked effect of buprenorphine-binding to μ -opioid receptors on gastrointestinal transit times, and indeed constipation seen in the clinic is remarkably low (Griessinger et al 2005). Buprenorphine also shows partial agonistic activity at the opioid receptor-like receptor 1 (ORL1)-receptors which are (at least at supraspinal receptors) postulated to induce a pronociceptive effect. A study by Lutfy et al (2003) reported that co-activation of ORL1-receptors compromises the antinociception induced by activation of the μ -opioid receptor. ORL1-activation has also an effect on hyperalgesia. It might be that buprenorphine's partial agonism reduces

this effect compared with full ORL1-agonists such as morphine or fentanyl. Buprenorphine's antagonistic action at the δ -receptors which have a marked anti-opioid action and seem to negatively modulate central analgesia seems further to contribute to its clinically seen analgesic effect. Its likewise antagonistic activity at the κ -opioid receptors might explain the fact that it induces much less sedation and psychotomimetic effects than morphine or fentanyl (Lewis 1985; Leander 1988). Animal studies have shown that buprenorphine has a 20–40 times higher potency than morphine (Martin et al 1976).

The strong binding of buprenorphine to the μ -opioid receptor has several consequences. Initial binding is relatively slow compared with other opioids such as fentanyl (Boas and Villiger 1985). However, the onset of analgesia is not dissimilar, since buprenorphine achieves effective analgesia at relatively low receptor occupancy (5%–10%) (Tyers 1980) and thus relatively low plasma concentrations of buprenorphine are sufficient to provide effective pain relief. The slow dissociation of buprenorphine from the receptor results in a long duration of effect and also confers another advantage in that when the drug is withdrawn an abstinence syndrome is rarely seen because of the long time taken for the drug to come off the receptor (Bickel et al 1988).

Pharmacokinetics

Due to the high first-pass effect (95%) seen after oral administration, Buprenorphine was initially available as either a parenteral or sublingual formulation. Onset of analgesia after sublingual administration has been shown to occur within 15 to 45 minutes with peak plasma concentrations reached after two hours (Bullingham et al 1980). The transfer half-life estimated at 76 minutes is consistent with a systemic availability completed within 5 hours. Average bioavailability with sublingual dosing was found to be 55% (McQuay et al 1986). The parenteral formulation of buprenorphine has a speed of onset within 5–15 minutes of either intravenous (IV) or intramuscular (IM) administration. As characteristic of lipophilic compound, buprenorphine exhibits multiphasic clearance; an initial rapid clearance followed by slower clearances observed after IV injection (McQuay and Moore 1995).

In the body, buprenorphine is highly protein-bound mostly to α -globulin and β -globulin fractions (Heel et al 1979). Since most drugs bind to albumin, there is no risk of competition for binding proteins, resulting in a lower risk

of interactions. Buprenorphine conjugates with glucuronic acid, which explains the low bioavailability of only 5% in the case of oral administration. In the liver, buprenorphine is metabolised to norbuprenorphine (N-dealkylbuprenorphine) and buprenorphine glucuronide. While the latter has no analgesic activity, norbuprenorphine exerts a weak analgesic action, but is of minor clinical importance (Ohtani et al 1995). After parenteral administration two thirds of the dose of buprenorphine is excreted unchanged in the faeces and one third is metabolised in the liver and eliminated as conjugates in the urine or bile (Heel et al 1979). In short-term treatment with buprenorphine, end-stage renal failure does not affect excretion of the drug.

Side effects

Buprenorphine has the typical side effects shown by all opioids including nausea, vomiting, dizziness, constipation, and headache. In a study of patients with chronic nociceptive pain, the analgesic efficacy of sublingual buprenorphine and sustained release morphine were similar, but the patients treated with buprenorphine had significantly fewer side effects (Bach et al 1991). This was particularly noticeable with respect to nausea, vomiting, and constipation and may in part be attributed to the sublingual route of administration bypassing the gut μ -opioid receptors. As with all other strong opioids, buprenorphine produces respiratory depression. In contrast with fentanyl and morphine, a ceiling effect has been shown to exist for buprenorphine-induced respiratory depression (Doxey et al 1982; Dahan et al 2005). This is consistent with the partial agonist profile of buprenorphine and the relevance of this factor with regard to the safety of the drug in clinical practice will be discussed later. The respiratory depressant effect of buprenorphine has been shown to respond to naloxone, an antagonist at the μ -opioid receptor, such that the effect can be completely reversed (Gal 1989; Dahan et al 2005).

Clinical efficacy

Buprenorphine is an effective analgesic with a potency at least 30 times that of morphine. The smallest dose recommended for IM use (0.3 mg) has been shown to be as effective as morphine (10 mg) but has a longer duration of action (6–18 hours) (Kay 1978). The accepted range for buprenorphine analgesic effects is 0.1–10 mg and in this range the drug behaves as an agonist with no flattening of the dose response curve at less than 100% effect. Buprenorphine given intravenously in the dose range of

0.4–7.0 mg for postoperative pain was found to be a potent, long-lasting safe analgesic with a minimum number of side effects, a dose-related efficacy and thus no ceiling effect for analgesia (Budd 1981).

The treatment of neuropathic pain represents a challenge to clinicians and there is controversy regarding the efficacy of opioids in this condition. The abnormal pain sensitivity caused by neuropathy including hyperalgesia and allodynia is often resistant to opioid therapy. Buprenorphine has been shown to have a pronounced antihyperalgesic effect. In contrast to pure μ -agonists, buprenorphine-induced antihyperalgesic effects have a significant longer half life compared with its analgesic effects (Koppert et al 2005). These findings might account for the clinical efficacy in pain states dominated by hyperalgesia and central sensitization such as postoperative pain or neuropathic pain. Clinically, it has been shown that IV buprenorphine is effective in the treatment of post-thoracotomy neuropathic pain, albeit at a higher dosage than required to treat nociceptive postoperative pain (Benedetti et al 1998). Further, buprenorphine is the only opioid where antinociception is not blocked by pertussis toxin which is an experimental model to study the pathophysiology of neuropathic pain (Womer et al 1997; McCormack et al 1999). Sublingual buprenorphine tablets have undergone extensive evaluation as analgesic agents for acute and chronic cancer-related pain and have additionally become a valuable agent with which to treat opioid dependency.

Transdermal delivery systems

Transdermal delivery systems (TDS) have now been used for more than 10 years in situations other than pain management and have been shown to provide effective and well-tolerated drug delivery (Berner and John 1994; Ly et al 2001). They are not suited for all drugs but have several advantages over traditional routes of administration, including noninvasive administration and rate-controlled drug release. The TDS formulation is designed to overcome the pharmacokinetic problems of both oral and parenteral opioids including poor gastrointestinal absorption, first pass metabolism and low bioavailability. This formulation is particularly useful for patients with pre-existing gastrointestinal problems and may improve patient compliance and quality of life. The high analgesic potency of buprenorphine, its high lipophilicity, and low molecular weight combined with a low abuse potential, make it an ideal drug for use in a TDS system. Together with another

opioid, fentanyl, buprenorphine is the only opioid available in a transdermal formulation.

The transdermal buprenorphine patch (Transtec®)

The transdermal buprenorphine patch, Transtec®, was first launched in Switzerland and Germany in 2001 and is now marketed all over Europe. Using matrix technology, buprenorphine is homogeneously incorporated in a solid polymer matrix patch which is applied to the skin. The adhesive buprenorphine patch is noninvasive and slowly and continuously releases the drug into the systemic circulation. This matrix patch structure avoids the risk of 'dose-dumping', a feature of older reservoir patch systems, which use a regulating membrane to restrict drug diffusion (Budd 2003). Transdermal buprenorphine is available in three different dosage strengths with total loading doses of 20 mg, 30 mg, and 40 mg designed to release buprenorphine at a steady controlled rate of 35 µg/h, 52.5 µg/h, and 70 µg/h, respectively. This corresponds to an administered daily buprenorphine dose of 0.8 mg/day, 1.2 mg/day, and 1.6 mg/day. The minimum effective concentration (MEC) for cases of moderate to severe pain is in the region of 100 pg/ml (Budd 2002). Pharmacokinetic studies have shown that after single application of the patch plasma levels of buprenorphine continuously increase and reach the MEC after 24 hours using the 35 µg/h patch and 12 hours using the larger 70 µg/h patch. (Sittl et al 2003). The initial recommendation on dose maintenance was that each patch remained effective for 72 hours. However, a recent open, randomised cross-over-study in chronic pain patients found that clinically effective plasma concentrations are reached after 24 hours and that these levels are maintained for the entire 96 hour application period (Likar 2005). The 96 hour buprenorphine TDS application was found to be bio-equivalent to the 72 hour application with regard to area under the curve (AUC) and concentration maximum (C_{max}). This allows twice weekly changing of the patch on fixed days (eg, always on Mondays and Thursdays), facilitating therapy for patients, increasing patient compliance, and rendering pain therapy more cost-effective.

Indications and dosing

Transdermal buprenorphine is indicated for the treatment of moderate to severe cancer-related pain and severe pain unresponsive to nonopioid analgesics, including neuropathic pain. It is not indicated for use in cases of acute pain.

Studies of the use of transdermal buprenorphine in patients with chronic tumor and non-tumor pain have shown that the patches achieved a good analgesic effect and reduced the need for additional oral analgesics. In addition, the quality of life of the patient was improved in comparison with conventional therapies, benefits including an increased duration of sleep (Likar et al 2003; Sittl et al 2003). A survey of 13 179 chronic pain patients of varying aetiologies including musculoskeletal, neurogenic, and cancer pain confirmed effective analgesia was provided by treatment with transdermal buprenorphine. Most of the patients had been pretreated with WHO step II or step III opioids, although 30% had not previously been prescribed any opioids. Pain relief was rated as good or very good by 81% of the respondents at the end of the observation period (Griessinger et al 2005).

In advanced cancer pain and the final stages of the disease nearly 50% of patients will require parenteral medicine (Zech et al 1995). In these cases, transdermal preparations such as transdermal buprenorphine or transdermal fentanyl offer noninvasive alternatives. A study of three patients with severe pain due to renal and metastasing prostate and breast cancer has shown buprenorphine TDS to be a valuable option, providing effective long-term treatment without dose escalation or compromise in tolerability (Schriek 2004). The efficacy and safety of buprenorphine 70 µg/h has been demonstrated in a trial in patients with chronic tumor-related pain requiring morphine 90–150 mg/day (Poulain et al 2005), demonstrating that transdermal buprenorphine works effectively in the high-dose range of morphine (ie, on step III of the WHO ladder) and is therefore a viable alternative to morphine.

Likar and Sittl (2005) reported that transdermal buprenorphine is very effective in patients with neuropathic pain or with pain having a strong neuropathic component when other opioids failed. The effectiveness of transdermal buprenorphine in neuropathic pain has also been investigated by Rodriguez et al (2004) in a study population of 237 patients (37% male, 63% female) who suffered from various typical neuropathic symptoms or pain syndromes where neuropathic pain constituted a major component. After 4 weeks treatment with transdermal buprenorphine, a clear decrease in the percentage of patients reporting moderate to severe pain and a corresponding increase in the percentage reporting none or only slight pain was documented. Although more studies are clearly needed in this area, it seems clear from already available data that buprenorphine

is one of the most promising opioids for the treatment of neuropathic pain.

The equipotency ratio of transdermal fentanyl to oral morphine has been established as 1:100 (Donner et al 1996). The comparable ratio for transdermal buprenorphine to oral morphine has been proposed to be 1:75, although clinical experience including data from postmarketing-surveys (Griessinger et al 2005; Muriel et al 2004) suggested that buprenorphine TDS may be more potent than initially suggested. A retrospective analysis in patients with both cancer and non-cancer pain has compared calculated equipotent oral morphine doses of transdermal fentanyl with equipotent morphine doses of buprenorphine prescribed in clinical practice and suggested that an equipotency ratio of 1:110 to 1:115, morphine to transdermal buprenorphine, may be more appropriate (Sittl, Likar, et al 2005).

Switching and combining with other opioids

The goal of pain management with opioids is to provide optimal analgesia with a minimum of adverse events. WHO guidelines on cancer pain recommend a switch of opioid if the current treatment is no longer of sufficient efficacy or if intolerable adverse events occur. Switching therapy to and from buprenorphine to or from other opioids does not present major problems.

It has been suggested that buprenorphine being a partial agonist at the same receptor site as morphine might block the effects of morphine if a patient was switched to morphine. Clinical studies have shown this not to be the case and in the analgesic dose range, a switch between buprenorphine sublingual (SL) and an equianalgesic dose of oral morphine sulphate was carried out without problems for the patient (Atkinson et al 1990). More recent animal studies involving combined use of buprenorphine and other opioids have indicated that a moderate antagonistic effect attributed to the partial μ -agonistic properties of buprenorphine was only seen when doses exceeded the therapeutic dose range, otherwise both morphine and fentanyl showed full efficacy (Koegel et al 2005).

Although morphine is considered to be the gold standard drug in pain management according to step III of the WHO analgesic ladder and may provide adequate analgesia for many patients, there are some who suffer from intolerable side effects and/or inadequate pain relief with morphine. Therefore a change also of formulation could be beneficial.

As a subanalysis of a large postmarketing survey on buprenorphine TDS found, patients who had been switched

from high daily doses of morphine (>120 mg) to at least $52.5 \mu\text{g/h}$ transdermal buprenorphine, benefited from an average 50% reduction in pain after the switch (Gruenthal, data on file, publication in preparation). In 70% of the patients this was achieved without the additional use of other opioid medication.

Concerns with long-term therapy

Tolerance development

Long-term use of opioids may lead to the development of tolerance requiring higher doses to be administered in order to produce a given level of response. Tolerance to analgesia may not be accompanied by tolerance to opioid-induced adverse effects so that dose escalation can often result in a negative impact on the adverse events profile.

The development of tolerance to opioids may be brought about by desensitization and down-regulation in μ -opioid receptors in response to agonist treatment. Both fentanyl and morphine have been shown to induce a loss of surface receptors, while buprenorphine was found to cause an increase (Zaki et al 2000). Although tolerance to buprenorphine may develop to many of its other effects as indicated in animal models, tolerance to its analgesic effects in chronic pain patients has not been shown (Robinson 2002).

A study of long-term management of chronic cancer and non-cancer pain showed that the proportion of patients needing 1 mg of sublingual buprenorphine daily in addition to the $35 \mu\text{g/h}$ patch remained essentially stable throughout the first 6 months of the study, which points to the dose stability of buprenorphine. In addition, 31% of patients were able to control their pain by using only one of the lowest dose patches throughout (Likar et al 2005). When treatment with transdermal fentanyl and buprenorphine TDS for at least 3 months was compared in a retrospective study on cancer and non-cancer patients, a significantly higher increase in mean daily doses of fentanyl compared with buprenorphine was found (Sittl, Nuijten, et al 2005).

Safety

Respiratory depression

Respiratory depression caused by opioids can be potentially life-threatening, but is much less of a problem with buprenorphine than with many other opioids including morphine, hydromorphone, methadone, oxycodone, and transdermal fentanyl (Dertwinkel et al 1998).

Buprenorphine has a ceiling effect associated with a bell-shaped dose response curve with regard to respiratory

depression, meaning that the risk to induce respiratory arrest does not linearly follow dose-increments of the substance. This ceiling effect provides a safety benefit in case of drug abuse (Doxey et al 1982). A comparison of the respiratory effect of intravenous buprenorphine and fentanyl in both animals and man confirmed a ceiling effect of buprenorphine, but not for fentanyl. In healthy human volunteers, fentanyl produced a dose-dependent depression of respiration with apnoea at doses $\geq 2.9 \mu\text{g/kg}$ while respiratory depression caused by buprenorphine levelled off at doses $\geq 3.0 \mu\text{g/kg}$ (Dahan et al 2005). A dose-response study in healthy male adult volunteers, showed that respiration was maximally depressed at doses of 16 mg of sublingual buprenorphine with a slightly reduced effect at 32 mg. Although 32 mg represents 70 times the recommended analgesic dose, this dose was well tolerated and produced no serious adverse effects (Walsh et al 1994). It is therefore more than unlikely that respiratory depression is caused by buprenorphine in the analgesic dose range. At very high doses (above 32 mg) it could occur. As with other opioids, it can be reversed by the μ -opioid antagonist naloxone, but due to buprenorphine's very tight binding to opioid receptors and its long-lasting effect, higher and repeated doses of naloxone would be necessary in these rare cases (Dahan et al 2005). Close monitoring of patients' respiration is recommended, especially in anesthetized or sleeping patients with repeated administration of very high doses of buprenorphine, but this should also be the case with any other μ -opioid agonist.

Renal impairment

Patients with renal insufficiency frequently require the use of opioids for painful syndromes not responsive to other therapies. This can be a problem particularly in the elderly where age-related changes can affect glomerular filtration, tubular secretion, and reabsorption of metabolites. Changes in renal function may affect the pharmacokinetics of opioids and necessitate a change in dosage (Mercadante and Arcuri 2004). Whilst morphine itself is largely unaffected by renal failure, accumulation of its active metabolite morphine-6-glucuronide cautions its use. Case reports of prolonged narcosis with both codeine and dihydrocodeine in renal insufficiency also call for care when using these agents (Davies et al 1996). The pharmacokinetics of buprenorphine are not altered in patients with renal failure (Summerfield et al 1985; McQuay et al 1986; Moore et al 1994). The main site for metabolism of buprenorphine is the liver, indicating that impaired renal function should have little influence on

plasma levels. The major metabolite of buprenorphine is norbuprenorphine. It has been found that levels of this metabolite may be raised after continuous intravenous dosing in patients with renal impairment. However, due to the lower potency and lower affinity of the metabolite for the receptor compared with the parent drug, it is unlikely that this is of any consequence (Hand et al 1990). A recent study of end-stage renal disease patients treated with buprenorphine TDS showed no elevated levels of buprenorphine or norbuprenorphine, indicating that a dose-adaptation in patients with end-stage renal disease is not necessary and analgesic effects of transdermal buprenorphine remain stable during treatment (Filitz et al 2005).

Hepatic impairment

The liver is the major site of biotransformation for most opioids, which raises the possibility that hepatic insufficiency may lead to reduced drug metabolism and the accumulation in the body. If metabolism is decreased the analgesic effect of the drug may be compromised. The major metabolic pathway for opioids is oxidation, exceptions being morphine and buprenorphine, which undergo glucuronidation. It has been shown that although oxidation of opioids is reduced in patients with hepatic cirrhosis resulting in reduced drug clearance, glucuronidation is less affected by liver disease (Tegeder et al 1999). The N-dealkylation of buprenorphine to norbuprenorphine is catalyzed by the cytochrome (CYP) P450 enzyme system, with CYP3A4 being the major isoenzyme. Since CYP3A4 protein expression is reduced in patients with severe chronic liver disease, patients with this condition should be closely monitored during treatment (Tegeder et al 1999).

Immunosuppression

Suppression of the immune system frequently occurs as a result of the trauma of surgery or from medical conditions such as HIV or cancer. In addition the elderly may be at particular risk due to the progressive declining function of the immune system as a consequence of ageing. Most strong opioids have been found to suppress the immune system to some extent within the antinociceptive range and careful selection of therapeutic agent is important particularly in patients who are already immunocompromised, including cancer patients at risk of metastatic dissemination. The acute administration of morphine has been shown in both animals and humans to significantly reduce cellular immunity and animals treated with morphine have shown an increase in

experimental infection and cancer. It is considered that opioid-induced immunosuppression is less relevant in chronic administration than in acute or short-time administration.

The immunosuppressive effect of opioids has been linked to μ -receptor agonism: opioids with high affinity for the μ -opioid receptor induce significant immunosuppression while those with κ -receptor or δ -receptor selectivity do not. Antagonists at the μ -opioid receptor tend to enhance the immune system (Budd 2004). The immunosuppressive effects of opioids are independent of their analgesic effects and appear to be a function of molecular structure. The opioids with lack of immunomodulatory capacity are buprenorphine, hydromorphone, oxycodone, oxymorphone, and tramadol all of which have a carbonyl substitution at C6 and a single bond between C7 and C8. An assessment of buprenorphine toxicity in rats indicated that buprenorphine may have a slight stimulatory effect on the immune system although the exact mechanism remains unclear (Van Loveren et al 1994). After 24 hours of administration of fentanyl in mice, key parameters for immune response were reduced including natural killer cell activity, lymphoproliferation, and interleukin-2 and interferon- γ production. By contrast, neither acute nor chronic administration of equianalgesic doses of buprenorphine produced any effect (Martucci et al 2004).

Special patient populations

Buprenorphine has been used in children in the past mainly in acute pain conditions such as postoperative pain where it proved to be safe and effective irrespective of the administration route (Maunuksele et al 1988a, 1988b; Kamal and Khan 1995; Olkkola et al 1995). Basically, the transdermal formulation is an ideal analgesic device for children as it is completely noninvasive and produces longlasting reliable analgesia. In addition, due to their matrix structure, patches can be cut into halves or quarters to allow for an easy adaptation to smaller dosing needs of younger patients. However, as there are as yet no data available in this patient group, transdermal buprenorphine is not licensed for children and young patients under the age of 18, and therefore cannot be recommended to be used in this group.

For the elderly, ie, patients above the age of 65 years, transdermal buprenorphine is an easy-to-use, safe, and effective analgesic device what has also been shown in the clinic (Griessinger et al 2005; Likar et al 2006, pers comm). In particular, buprenorphine's low potential for drug-drug-

interactions (see chapter on Interactions), its beneficial effects on the immune system, and in patients with renal impairment, make it the opioid of choice for pain treatment in elderly patients.

Tolerability

Gastrointestinal adverse events associated with strong opioid use include nausea, vomiting, and constipation. None of these conditions present a severe medical risk and can normally be dealt with by the clinician. Buprenorphine has a low incidence of adverse events in practice. Following parenteral use, the incidence of nausea is 8.8% and the incidence of vomiting is 7.4% (Harcus et al 1979). Continuous sublingual use in chronic pain has found that the incidence for nausea falls to 6.5% and for vomiting to 3.5% (Bach et al 1991).

Constipation is another commonly encountered side effect of opioid use that can significantly affect quality of life, particularly for elderly patients. The incidence of constipation with buprenorphine has been shown to be lower than with morphine use (Bach et al 1991). In a study of sublingual administration of buprenorphine in 51 elderly patients with chronic pain, only one patient reported constipation (Nasar et al 1986). Bypassing the gut μ -opioid receptors through the use of parenteral or transdermal preparations of opioids may offer advantages in this respect.

Central nervous system (CNS)-related adverse events including dizziness, drowsiness, and euphoria may occur at the start of opioid treatment or following an increase in dosage. The incidence is directly linked to kidney function. Any opioid that is mainly excreted by the renal route will accumulate in patients with renal impairment and has the potential to cause an increase in the incidence of adverse events. This situation is particularly relevant in the elderly, a group in whom renal function may decline often even unrecognised with increasing age. As only approximately 15% of buprenorphine is excreted by the kidneys the likelihood of accumulation is low in comparison with either morphine or fentanyl, where 75% or more is excreted by the renal route. Buprenorphine has a lower risk of CNS-related adverse effects than other opioids.

Interactions

A drug-drug interaction occurs when the effect of a particular drug is modified by another drug taken concomitantly. This is a situation that may be of particular concern in the elderly where reduced renal function and multiple drug therapy are often combined. Competition for

binding sites on plasma proteins such as albumin and α - or γ -globulins may cause reduced binding and hence increased levels of unbound drug, which may cause an increased pharmacological effect. The pharmacological profile of buprenorphine is favourable in this respect since 96% is bound to α - or γ -globulins whereas most other drugs bind to albumin.

Many drugs are metabolised in the liver by the cytochrome P450 system and those that act as either inducers or inhibitors of this enzyme system may cause clinically important drug interactions. Buprenorphine has been demonstrated to inhibit CYP3A4- and CYP2D6-mediated reactions, however, at therapeutic concentrations it is unlikely that either buprenorphine or its metabolite norbuprenorphine would cause significant interactions with other CYP-metabolised drugs (Umehara et al 2002; Zhang et al 2003).

However, all opioids interact with other CNS-depressant drugs, eg, benzodiazepines, and this might result in an increased risk of centrally-mediated side effects such as sedation or respiratory depression. This effect is most likely due to a synergistic pharmacodynamic effect on the CNS and not to hepatic metabolism (Ibrahim 2000). There is a respective class label warning in the summary of product characteristics (SmPCs) of transdermal buprenorphine and of all other strong opioids.

Dependence, addiction, and abuse potential

Fear of dependence and addiction is one of the main reasons why many clinicians have in the past been reluctant to prescribe opioids. As a drug class, therapeutic doses of opioids are safe and non-toxic even under chronic dosing conditions. Supratherapeutic doses of μ -opioid agonists can be lethal, especially when administered to non-tolerant individuals. This toxicity is mainly due to the respiratory depressant action. As previously discussed, in contrast to many other opioids buprenorphine shows a ceiling effect with respect to respiratory depression that contributes to its safety profile. Reports of episodic cases of buprenorphine abuse have largely been confined to experienced drug abusers. The abuse potential of buprenorphine, although low, is further reduced in a transdermal preparation because the plasma levels slowly rise to a therapeutic level, unlike the rapid peak level that occurs with other formulations.

There is little evidence that buprenorphine has the potential to cause dependence and addiction. Even after prolonged treatment with buprenorphine withdrawal symptoms after spontaneous withdrawal are relatively

moderate compared with those that occur after comparable treatment schedules with opioids such as morphine, fentanyl, or methadone (Tzschentke 2002; Walsh and Eissenberg 2003). This property is probably related to the receptor kinetics of the drug, as dissociation occurs very slowly once bound to the μ -opioid receptor. The long duration of action of buprenorphine (and hence need for less frequent dosing) has suggested its use in the treatment of opioid addiction. Buprenorphine has been shown to be capable of blocking the effects of 120 mg doses of morphine, a blockage that persisted for 29.5 hours (Jasinski et al 1978). Buprenorphine in sublingual form has been found to be acceptable to addicts, and its limited withdrawal effects makes a gradual reduction in the dose of buprenorphine taken more likely.

The advantages of transdermal buprenorphine for long-term therapy

The treatment of chronic pain frequently requires long-term therapy that may continue for many months or even years. Transdermal buprenorphine offers an easy to use formulation which can maintain therapeutic serum levels for up to 96 hours. The availability of sublingual buprenorphine tablets for use as supplementary medication in breakthrough pain episodes is in line with the WHO recommendation for an immediate release formulation containing the same substance for rapid pain relief if required.

In terms of handling, transdermal buprenorphine offers a number of advantages. The patch can be applied by the patient or carer, it is unobtrusive and sticks on well over the full dosage period. In a study of 239 chronic pain patients who used buprenorphine TDS for a mean period of 7.5 months, 93.3% rated handling of the patch as "without problem" (Likar et al 2005). Buprenorphine TDS can be used by patients with swallowing difficulties and results in less tablet intake, an important feature for the elderly who may need mostly orally applied co-medication. It should be kept in mind that due to buprenorphine's high affinity for the μ -opioid receptor and its long duration of action, newly applied analgesics may not work until the clinically relevant doses of buprenorphine level off after the final removal of buprenorphine patches. During continuous therapy with buprenorphine patches, this long duration of action of buprenorphine is not a problem as the newly applied buprenorphine patches need 12–24 hours until clinically relevant plasma levels are reached.

Analgesic gaps are therefore unlikely as long as proposed dosing schemes are followed, and transdermal bupren-

orphine provides an effective and sustained dose-dependent analgesia irrespective of patient age or pain syndrome. A number of studies have been conducted to assess the analgesic efficiency and tolerability of buprenorphine TDS in long-term management of cancer and non-cancer pain. In the long-term study referred to above (Likar et al 2005), 90% of the 239 patients (age range 27–86 years; mean 68 years) reported at least satisfactory pain relief. Forty-three percent of patients rated their pain relief as good and complete. In a post-marketing surveillance study over a total period of 9 months in 13 179 patients with cancer and non-cancer pain (age range 13–101 years; mean 68 years), 81% reported pain relief to be “good” or “very good” at the end of the study, whereas only 6% of the study population considered that their previous analgesic treatment fell into these categories (Griessinger et al 2005). The demographics of this study emphasize the efficacy of buprenorphine TDS in a wide range of pain conditions. The patient population in this study included 3690 (28%) with cancer pain, the most common specific diagnosis being lower respiratory tract cancer, urogenital cancer, and breast cancer. Metastases were present in 15% of cancer patients. Among the 9489 patients suffering from non-cancer pain, musculoskeletal pain was the most frequently reported condition (77%), predominantly back pain and joint/rheumatic pain. Neurogenic pain (23%) was mainly a result of neuralgias, neuropathies, or phantom pain.

In the long-term study (Likar et al 2005), patients were allowed to control pain by sublingual buprenorphine tablets as needed. The proportion of patients needing 1 mg buprenorphine daily (ie, one tablet in addition to the patch) remained remarkably stable throughout the first 6 months of the study indicating dose stability of buprenorphine under long-term conditions. In another postmarketing surveillance study on transdermal fentanyl in cancer patients over a period of 4 months, it was found that most patients required a dose increase during the observation period, the median dose increasing from 1.2 mg/day to 2.4 mg/day (Radbruch et al 2001).

The transdermal application reduces the occurrence of adverse events since the plasma buprenorphine concentration remains stable. In the post-marketing surveillance study of buprenorphine use, out of a total of 13 179 patients, 520 (4%) experienced nausea and 210 (1.6%) experienced vomiting. Constipation was reported in 1.0% of the subjects. A subgroup analysis of elderly patients (>60 years) found little change in this value (1.1%) (Griessinger et al 2005). This compares favourably with a survey of the use of

transdermal fentanyl in 1005 patients (mostly with cancer pain) where the incidence of constipation was 4% (Radbruch et al 2001).

Buprenorphine has a lower risk of CNS-related adverse events than other opioids. A comparison of the two surveys mentioned above found the incidence of CNS effects in patients receiving long-term transdermal buprenorphine was lower than in patients receiving long-term transdermal fentanyl. Somnolence, hallucinations, vertigo, and convulsions were experienced by 0.8%, 0.009%, 0.002%, and 0.001% of the subjects in the buprenorphine survey but by 4.0%, 0.2%, 1.0%, and 0.1%, respectively, in the fentanyl survey. One and half percent of the buprenorphine patients reported dizziness (data unavailable in fentanyl patients) which may in some instances respond to a dopamine antagonist.

Local skin reactions at patch site may occur and clinical trials have shown that such occurrences are irrespective of whether buprenorphine or placebo were involved. These reactions are most likely due to patch material or adhesive. In a study comparing three different dose strengths of buprenorphine TDS with placebo, patch application was well tolerated, only 10% to 20% of all subjects in all four groups reported local adverse events, but these were not statistically significant. Local skin reactions, predominately consisted of mild to moderate erythema or pruritus lasting less than 24 hours (Böhme and Likar 2003). In a long-term study of buprenorphine use, local skin reactions at the patch site occurred in 20.5% of patients. Most frequently these were erythema (12.1%), pruritus (10.5%), and exanthema (8.8%) (Likar et al 2005). In the post-marketing surveillance study, the overall occurrence of local adverse effects was much lower. Contact dermatitis was seen in only 0.8% of the subjects and pruritus in only 0.7% (Griessinger et al 2005).

Adherence to therapy or compliance is a major prerequisite for therapeutic success in the treatment of chronic pain. Convenient drug handling and limited side effects are key points in ensuring patient compliance. The study of the extended wearing time has resulted in the registration of the patch for a duration of application of up to 4 days (96 hours) allowing regular patch changes on 2 fixed days a week (Likar 2005), which is easier to remember for elderly patients and carers. In the post-marketing surveillance study, patient compliance at the end of the observation period was 91%. The fact that 70% of the patients continued with buprenorphine TDS after completion of the study indicates that it is not only effective, but also easy and convenient to use (Griessinger et al 2005).

Conclusions

Buprenorphine has been widely used and studied for over 20 years and shown to be an effective opioid analgesic. The μ -agonistic profile of buprenorphine, combined with high analgesic potency and efficacy, good safety profile, ease of opioid switch, and reversibility by μ -antagonists makes this drug a valuable option for long-term treatment in a wide range of chronic pain indications. By using the transdermal formulation of buprenorphine, the rate of drug delivery can be controlled and stable plasma concentrations achieved. The transdermal administration route is an advantage for long-term use in ease of handling, increased patient compliance, and cost-effectiveness of treatment.

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