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Review

Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine

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ABSTRACT

Buprenorphine was not used widely in clinical practice over many years, mainly due to analgesic potency and clinical safety concerns based on misinterpreted animal data. Contrary to previous concerns, however, no analgesic ceiling effect and no antagonism of combined pure μ-opioid receptor agonists is seen within the therapeutic dose range. In recent studies, buprenorphine could be effectively and safely combined with full μ-agonists, and switching between buprenorphine and another opioid provided comparable pain relief based on equianalgesic doses. Moreover, buprenorphine exerts an antihyperalgesic effect, which is due—at least in part—to antagonistic activity at κ-opioid receptors.

Buprenorphine pharmacokinetics are not altered by advanced age or renal dysfunction. In addition, the risk of respiratory depression is lower than with other opioids including morphine, hydromorphone, methadone and fentanyl. Unlike morphine and fentanyl, there is no immunosuppressive activity with buprenorphine at therapeutic analgesic doses. Transdermal buprenorphine has significantly improved the clinical use of the drug, providing continuous buprenorphine release for up to 96 h. In clinical trials, patients receiving transdermal buprenorphine experienced significantly greater pain relief, better sleep, and a reduced need for rescue therapy, compared to placebo. Large-scale post-marketing studies have confirmed the effectiveness of transdermal buprenorphine in treating moderate-to-severe cancer and non-cancer pain including neuropathic syndromes. Finally, the comparably low incidence of CNS adverse events and constipation, and the possibility of use in severe renal dysfunction without a need for dose adjustment make buprenorphine well suited for chronic pain management in at-risk patients, such as diabetics, elderly or renally impaired individuals including those requiring haemodialysis.

1. Introduction

Chronic pain represents a significant challenge to the patient and the physician (Becker et al., 1997). Some 70% of cancer patients and 85% of those suffering from cancer-related pain will eventually require management with opioids (Higginson, 1997; Fine et al., 2004; Foley, 2000), which have become the mainstay of cancer pain treatment (WHO, 1996). In the treatment of moderate-to-severe non-cancer pain, the use of strong opioids is also increasing (Breivik et al., 2006; Portenoy et al., 2007), with proven benefits in inflammatory, ischaemic, visceral, musculoskeletal or even neuropathic pain (Lilleso et al., 2000; Rowbotham et al., 1991; Roth, 1998). In a recent systematic review of the literature (Martell et al., 2007), the overall opioid prescribing rates for chronic back pain varied widely by treatment setting (3–66%). An analysis of the National Ambulatory Medical Care Survey (NAMCS) data from 1980 versus 2000 revealed an increase in the use of potent opioids for chronic musculoskeletal pain from 2% to 9% of visits (Caudill-Slosberg et al., 2004). Although several clinical trials showed proven benefits of opioids in a certain, not well defined portion of non-cancer pain sufferers, simply extrapolating these short-term data to long-term clinical use of opioids in such patients remains controversial (Fields, 2007).

Effective long-term pain relief requires minimal variation in opioid plasma levels to prolong the duration of analgesic action and reduce potential adverse effects. The introduction of slow release, transdermal drug delivery systems—so-called opioid patches—offered a number of advantages over oral and parenteral routes (Caplan and Southam, 1990; Grond et al., 2000; Zech et al., 1995; WHO, online). By providing rate-controlled delivery with stable plasma concentrations, more effective analgesia and fewer adverse events (Caplan and Southam, 1990), they reduce the need for frequent dosing, are more convenient for patients and physicians, and increase treatment compliance (Grond et al., 2000; Zech et al., 1995).

Buprenorphine, a partial μ-opioid receptor agonist, was introduced in Europe more than two decades ago in both parenteral

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and sublingual formulations. Although it has been shown to be effective in the treatment of acute and chronic pain, and has been indicated for the management of moderate-to-severe pain (Heel et al., 1979), sublingual buprenorphine was not used much in clinical practice, mainly owing to a widespread underestimation of its analgesic potency and some safety concerns based on the misinterpretation or over-interpretation of experimental animal data. Buprenorphine, therefore, has not even been mentioned in some national and international guidelines developed with the aim of optimizing pain control. Meanwhile, the proven analgesic potency of buprenorphine (Johnson et al., 2005; Sittl et al., 2005), and its good lipophilicity (McQuay et al., 1986) made it an ideal candidate for transdermal delivery. Consequently, a transdermal matrix patch formulation of buprenorphine (Transtec®) was developed (Evans and Easthope, 2003). Since transdermal buprenorphine has been on the market, new clinical and preclinical data have become available about this drug, although the overall clinical evidence, particularly in relation to efficacy and tolerability, is still limited, as there were not so many high-grade clinical studies conducted so far. This topical review provides an updated overview of the current insights into the pharmacological properties of transdermal buprenorphine, in particular on the recent experimental and clinical data relevant to the treatment of chronic cancer and non-cancer pain in clinical practice.

2. Pharmacology of buprenorphine

Buprenorphine is a semi-synthetic derivative of the opium alkaloid thebaine, which is found in the poppy *Papaver somniferum*. Its chemical structure contains the morphine skeleton, but with some significant differences (e.g. a cyclopropylmethyl group) (Fig. 1), and gives buprenorphine the general characteristics of morphine along with its own specific pharmacological and clinical features (Flippen-Anderson et al., 1994). Based on the different formulations and depending on the pain model and the route of application, buprenorphine has been reported to be about 25–100 times more potent than morphine (Atkinson et al., 1990; Jasinski et al., 1978; Sittl et al., 2005; Sittl, 2005), which means that, according to the latest conversion calculations for buprenorphine to morphine, an equipotency ratio of 1:110–1:115 is assumed to provide the same degree of analgesia (Sittl et al., 2005).

2.1. Pharmacodynamics

2.1.1. Receptor-binding

Buprenorphine is a centrally-acting analgesic, and its clinical actions result from binding to the opioid receptors (Cowan et al., 2005). The drug acts as a so-called partial μ-opioid receptor agonist as well as a κ-opioid receptor antagonist, and binds to these receptors with high affinity. Buprenorphine slowly dissociates from μ-opioid receptors, which results in a slow onset but relatively long duration of analgesic action (Jasinski et al., 1978).

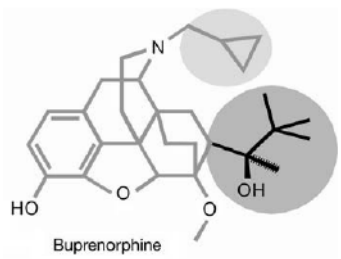

Fig. 1. Buprenorphine chemical structure. Structure outside the shaded areas = morphine-like structure.

Previous misconceptions regarding an analgesic 'ceiling effect' (bell-shaped dose response curve) with buprenorphine have led to reservations over its clinical use. However, these reservations have arisen from data obtained in animal pain models, in which buprenorphine was used at very high doses, far beyond the analgesic dose range. Recently, a systematic comparison of the potency and efficacy of buprenorphine in multiple animal models was conducted in parallel in the same laboratory, and disproved the former beliefs (Christoph et al., 2005). Besides the fact that the interpretation of the 'bell-shaped' (or 'inverted U-shaped') dose–response curve is still a matter of intensive academic speculation, a 'bell-shaped' response curve has never been observed in humans. In contrast, a dose–linear response without any 'ceiling effect' has been demonstrated within the therapeutic analgesic dose range in humans (Budd, 2002; Dahan et al., 2006) (Fig. 2).

2.1.2. Interaction with μ-opioid agonists

In interaction experiments using the tail-flick test, the combination of morphine and buprenorphine within their respective analgesic dose ranges produced an additive response, irrespective of whether buprenorphine was administered before or after morphine. In animals pre-treated with an analgesic threshold dose of buprenorphine, the addition of morphine, oxycodone or hydromorphone resulted in an additive or even supra-additive (synergistic) effect (Cowan et al., 2005; Kögel et al., 2005) (Fig. 3). Similar results were obtained when the administration of buprenorphine was preceded by a full μ-agonist. These data suggest that, in fact, buprenorphine, at clinical doses, behaves like a full μ-agonist.

Switching from buprenorphine to other μ-agonists and vice versa has also been demonstrated to work in animal models (Kögel et al., 2005). Although buprenorphine is associated with slow receptor dissociation *in vitro*, *ex vivo* binding studies in rats have shown reversible receptor occupancy within the duration of analgesic action (Englberger et al., 2006). In one study, μ-opioid receptor-binding capacity in brain homogenate was determined at different time intervals after buprenorphine administration (Englberger et al., 2006). Whereas after 1 h, 90% of receptors were occupied, full binding capacity was gradually restored within 8 h. The time course for receptor occupancy mirrored more or less the duration of the analgesic effect, which shows that opioid receptor re-occupancy can occur within the period of analgesic action of buprenorphine, and that no refractory period is expected between the

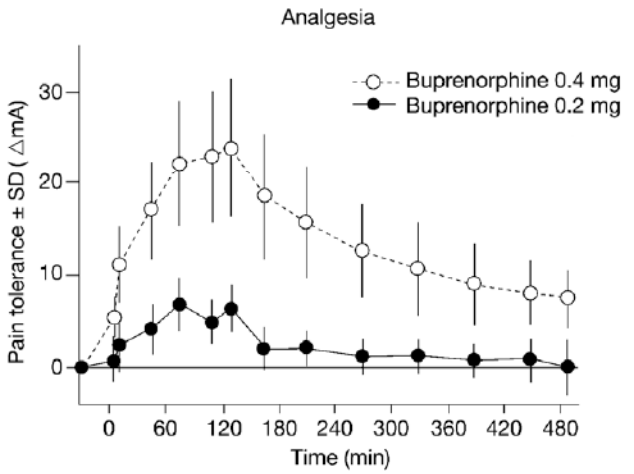

Fig. 2. Influence of i.v. buprenorphine 0.2 mg and 0.4 mg (per 60 kg) on pain tolerance in healthy volunteers (Dahan et al., 2006). Values are the increase in currents to achieve pain tolerance relative to baseline pain tolerance currents (ΔmA). A significant increase in analgesia was observed going from buprenorphine 0.2 mg to 0.4 mg.

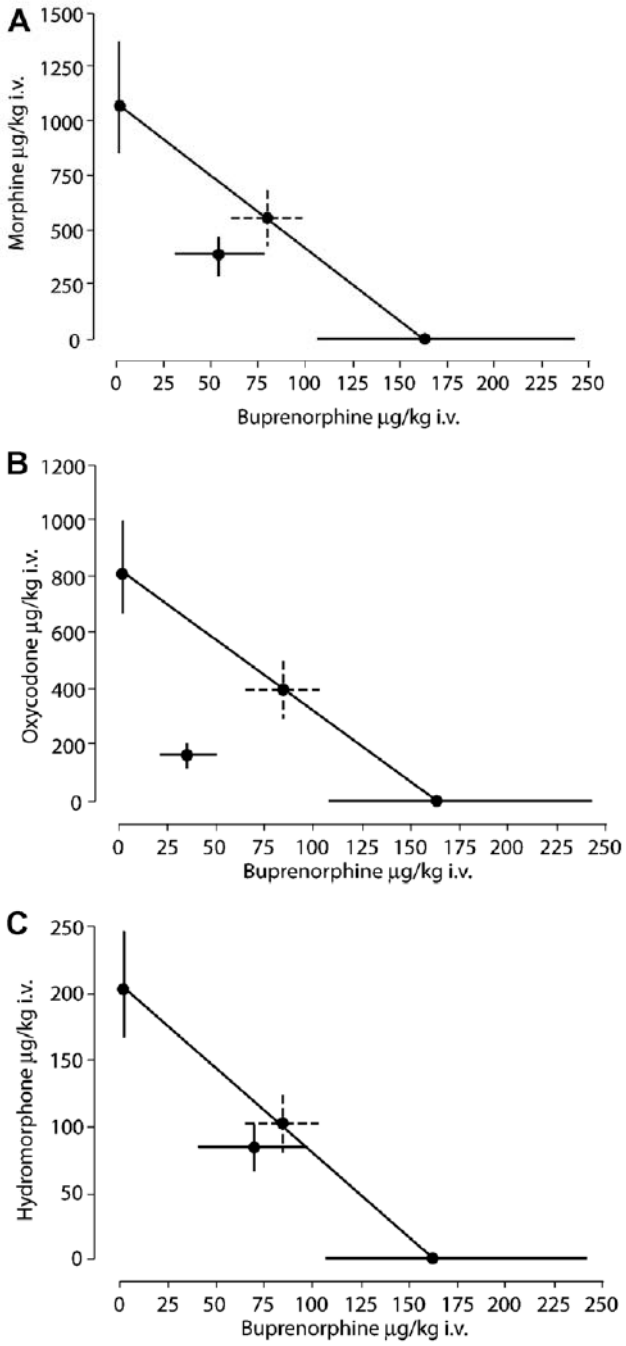

Fig. 3. The effect of buprenorphine pre-treatment on the antinociception induced by (A) morphine or (B) oxycodone or (C) hydromorphone in the tail-flick test (Kögel et al., 2005). Combinations of equipotent doses were tested and the ED_{50} values were compared with the theoretically additive ED_{50} value. There was a significant difference ($p < 0.001$) between experimental and theoretical additive ED_{50} values only in (B).

subsidence of buprenorphine analgesia and the onset of action of the new opioid. In a tail-flick study, mice were treated with a full antinociceptive dose of buprenorphine followed by half-maximal analgesic doses of morphine or fentanyl after the effect of buprenorphine had worn off. Again, buprenorphine pre-treatment had no effect on morphine- or fentanyl-induced antinociception (Cowan et al., 2005). The slow receptor kinetics of buprenorphine, therefore, do not have any detrimental effect on μ-opioid receptor availability beyond the duration of its analgesic action (Cowan et al., 2005). Clinical data from post-marketing surveillance studies clearly confirm these experimental findings (Barutell, 2004; Muriel, 2004; Griessinger et al., 2005).

2.1.3. Respiratory depression and naloxone reversal

The risk of respiratory depression is low with buprenorphine and is rarely of clinical relevance (Dahan et al., 2005, 2006; Dahan, 2006), as long as no additional CNS-depressant drugs are coadministered. A Medline® search-based review of clinical studies indicated that respiratory depression occurred less frequently with buprenorphine (none in 418 patients) than with morphine (19 out of 3745, or 0.5%), hydromorphone (1 out of 183, or 0.5%), methadone (6 out of 150, or 4%) or transdermal fentanyl (9 out of 388, or 2.3%) (Dertwinkel et al., 1998). A study in healthy volunteers showed that following intramuscular buprenorphine (dose range 0.15–1.2 mg) the risk of respiratory depression increased linearly, but the respiratory effect did not reach a clinically significant degree (Orwin, 1977). Furthermore, the respiratory effect of buprenorphine has been shown to be limited by a 'ceiling effect' at high doses not only in animals (Doxey et al., 1982; Dahan et al., 2005; Yassen et al., 2005), but also in human volunteers (Budd, 1981; Dahan et al., 2005, 2006; Dahan, 2006; Walsh et al., 1994; Walsh et al., 1995). In a clinical study evaluating the effect of high-dose intravenous buprenorphine (0.4–7.0 mg) in 50 postoperative patients over a 24 h period, no respiratory depression could be observed (Budd, 1981). Respiratory depression in opioid-experienced (but not physically-dependent) patients after sublingual buprenorphine (1–31 mg) reached a plateau at doses ⩾8 mg (Walsh et al., 1994). In a group of healthy volunteers the buprenorphine-induced respiratory depression demonstrated ceiling at doses above 0.1 mg/70 kg body weight (Dahan et al., 2005). In this industry-sponsored study, ventilation at a fixed end-tidal P_{CO_2} reached maximum peak depression of about 50% of baseline under buprenorphine, whereas fentanyl showed irregular breathing and apnea at comparable doses (0.1 mg/70 kg). These human data confirmed experimental studies in rats, showing the occurrence of ceiling in respiratory depression but not in antinociceptive efficacy of buprenorphine (Dahan et al., 2005; Yassen et al., 2005). Recently, the same group demonstrated in healthy young volunteers that two incremental i.v. doses of 0.2 and 0.4 mg buprenorphine increased significantly the antinociceptive effect, while buprenorphine-induced respiratory depression showed a similar magnitude and time course for the two i.v. doses tested. The authors concluded, that over a dose range from 0.05 to 0.6 mg i.v. burprenorphine displays ceiling in respiratory depression, but not in analgesic efficacy.

In a similar study directly comparing the respiratory effects of fentanyl (1.0–7.0 μg/kg) and buprenorphine (0.7–9.0 μg/kg) in healthy opioid-naive volunteers, an obvious ceiling effect was shown at clinical buprenorphine doses ranging between 0.2 and 0.4 μg/kg or greater (Dahan et al., 2005; Dahan, 2006). Whereas fentanyl led to a dose-dependent increase in respiratory depression finally resulting in apnoea at doses ⩾3.0 μg/kg, buprenorphine only produced mild-to-moderate respiratory depression that levelled off to about 50% of baseline at doses ⩾2.0 μg/kg and never induced apnoea. The results from animal experiments indicate that the respiratory effect ceiling occurs at a much lower dose (>0.2 mg/kg) than the analgesic effect ceiling (which requires doses higher than the therapeutic dose range) (Dahan et al., 2005, 2006; Yassen et al., 2005).

Thus, all experimental and clinical data do support the idea that there is a limit on the respiratory depressant action of buprenorphine, and that the maximum depressant effect does not pose a significant medical risk, when buprenorphine is used alone and under therapeutic conditions. In combination with other CNS-depressant drugs, however, this "built-in" safety of buprenorphine may disappear.

Importantly, any buprenorphine-induced respiratory depression could be fully reversed by repetitive doses (⩾1 mg each) or a continuous infusion of high-dose naloxone (Dahan, 2006). After a 0.2 mg buprenorphine infusion, 95% reversal was achieved at a total naloxone dose of 5.4 mg (half as a bolus, the remainder as an infusion over 30 min). Single naloxone bolus administration led only to a partial and short-lived reversal followed by renarcotization and, thus, cannot be recommended. In case of an inadvertent respiratory depression, a bolus dose of 2 mg naloxone over 90 s followed by a continuous infusion with 4 mg/h for up to 90 min should be applied.

2.1.4. Drug dependence and tolerance development

All centrally-acting opioids have a certain risk of physical dependence and abuse. Of course, after long-term treatment with buprenorphine, withdrawal symptoms cannot be excluded, but they are usually mild in intensity with a delayed onset after more than 72 h. They appear to be milder than those associated with morphine and fentanyl (Jasinski et al., 1978; Heel et al., 1979; Walsh and Eissenberg, 2003). As with other opioids, the severity of symptoms, which include agitation, anxiety, nervousness and sleeplessness, can be minimised by a slow gradual dose reduction (Jasinski et al., 1978; Heel et al., 1979; Walsh and Eissenberg, 2003).

Based on extensive studies of its use in opioid supervised withdrawal and as a maintenance agent (Mello and Mendelson, 1980; Walsh and Eissenberg, 2003), buprenorphine has been approved for the treatment of opioid dependence in a number of countries, notably France, as well as other European Union countries, Australia, and the United States of America. In non-dependent opioid abusers, even high doses of buprenorphine (up to 16 mg i.v. or 32 mg sublingual) produced little or no respiratory depression (Walsh et al., 1994, 1995). However, recently also deaths involving i.v. buprenorphine overdose in combination with benzodiazepines and other drugs have been reported in polysubstance abusers from France (Kintz, 2001).

Due to its slow dissociation from the μ-receptor and the resulting milder withdrawal symptoms, the risk of the development of drug dependence and analgesic tolerance in the short- or long-term seems to be lower with buprenorphine than with full μ-opioids (Heel et al., 1979; Robinson, 2002; Walsh et al., 1995; Walsh and Eissenberg, 2003). Results from several laboratory studies consistently showed that the spontaneous buprenorphine withdrawal syndrome, when observed, appeared after several days following abrupt termination of buprenorphine treatment and was usually described as mild to moderate in intensity (for review see Walsh and Eissenberg, 2003).

Unlike other opioids, buprenorphine does not induce μ-opioid receptor internalization, which leads to a loss of receptors on the neuronal cell surface. An *in vitro* study comparing the effects of fentanyl, morphine and buprenorphine on the density of cell surface μ-opioid receptors showed that buprenorphine actually increased the number by 10%, compared to a 35% and 9% reduction with fentanyl and morphine, respectively ($p < 0.05$ *versus* control) (Zaki et al., 2000). This may further explain why the risk of tolerance development is comparatively low with buprenorphine.

The partial agonist activity of buprenorphine limits the magnitude of the effects that might induce drug abuse (Walsh and Eissenberg, 2003). When higher doses of buprenorphine are tested, the partial agonist profile is revealed as a flattening out of the dose-effect curve, i.e. increasing doses do not result in greater increases of subjective measures. However, more recent data suggest that also buprenorphine can function as a reinforcer and does possess some abuse potential at therapeutic doses, but only when intravenously self-administered in non-dependent individuals with histories of opioid abuse (Comer et al., 2002).

In conclusion, as extensively reviewed elsewhere (Walsh and Eissenberg, 2003), the partial μ-agonist profile and low intrinsic activity contribute to the good safety profile of buprenorphine, its decreased abuse potential, and its ability to suppress opioid withdrawal while limiting the physical dependence produced by buprenorphine maintenance treatment.

2.1.5. Opioid-induced hyperalgesia

Even a brief exposure to certain opioids can induce long-lasting hyperalgesia (Koppert et al., 2001). Buprenorphine, however, has demonstrated an antihyperalgesic effect that lasts longer than the analgesic effect in a human pain model (Koppert et al., 2005). This is in contrast to full μ-agonists (Koppert et al., 2005; Tröster et al., 2004) (Fig. 4). In these human experimental pain models, the mechanism for this pronounced antihyperalgesic effect of buprenorphine is yet unclear, but it has been shown that κ-receptor agonists promote hyperalgesic pain states and antinociceptive tolerance (Vanderah et al., 2000). Thus, it has been speculated that buprenorphine may exert its antihyperalgesic effects via its antagonism at the κ-receptor (Koppert et al., 2005).

Antihyperalgesic effects of buprenorphine have also been demonstrated by case reports of successfully treated neuropathic pain syndromes with a strong allodynic/hyperalgesic component (Likar and Sittl, 2005; Likar et al., 2003; Louis, 2006), when other

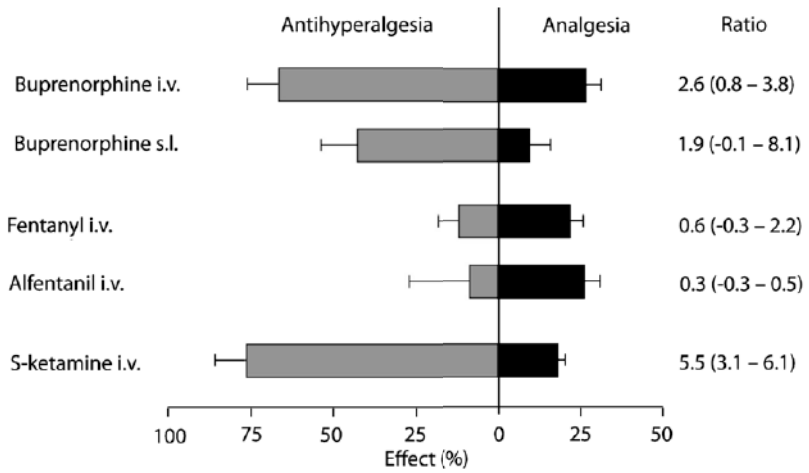

Fig. 4. Ratios of antihyperalgesic and analgesic effects after application of the respective medication, based on the areas under the curve of the individual ratings (AUC antihyperalgesia/AUC analgesia) (Koppert et al., 2005). *Key*: i.v. = intravenous; s.l. = sublingual. The data for fentanyl, alfentanil and S-ketamine are re-analysed from previous studies (Koppert et al., 2001; Tröster et al., 2004). Data are expressed as mean and SD.

μ-opioids had failed. These preliminary observations suggest that mechanisms involved in hyperalgesia and neuropathic pain might be more susceptible to buprenorphine than to other opioids. However, as the variable sensitivity of neuropathic pain to opioids is only incompletely understood, controlled comparative clinical trials are required to further evaluate this observed phenomenon.

2.1.6. Immune suppression

In animal experiments, buprenorphine does not exert immunosuppressive activity at analgesic doses (Van Loveren et al., 1994). This is in contrast to morphine which has been repeatedly shown to be a strong suppressor of various components of the immune system (Fecho et al., 1996; Sacerdote, 2006). The immunosuppressive effects of morphine and fentanyl have been clearly observed and described in animals as well as in the human, both in healthy volunteers and in patients (Franchi et al., 2007). The few data present in the literature on the immunological effects of buprenorphine in the human mainly refer to maintenance treatment of drug abusers (Neri et al., 2005), in whom a safe immunological profile of buprenorphine was observed.

The chemical properties of buprenorphine, i.e. its antagonism at the κ-opioid receptor, are thought to be partly responsible for the lack of immunosuppression (Evans and Easthope, 2003). In a study at the periacqueductal gray of the rat mesencephalon, the indirect neurohumoural effects of buprenorphine and morphine on the immune system were investigated. In contrast to morphine, which significantly suppressed these immune functions (Gomez-Flores and Weber, 2000), buprenorphine did not result in any functional changes of splenic natural killer (NK) cells, T-lymphocytes or macrophages. In another animal study comparing the effects of buprenorphine and fentanyl in mice, chronic buprenorphine administration, unlike fentanyl, did not show any significant influence on immune parameters important for antimicrobial defence or anti-tumor surveillance (lymphoproliferation, NK lymphocyte activity, cytokine production, lymphocyte counts) (Martucci et al., 2004).

Recently, the effects of equianalgesic doses of buprenorphine (0.1 mg/kg), fentanyl (0.1 mg/kg) and morphine (10 mg/kg) were investigated on the hypothalamus–pituitary–adrenal (HPA) axis, natural killer (NK) cell activity and metastatic colonization in rats (Franchi et al., 2007). Whereas in normal animals morphine and fentanyl stimulated the HPA axis, decreased NK cell activity and augmented tumor metastases, buprenorphine was void of these effects. Moreover, only buprenorphine was able to prevent the neuroendocrine and immune system alterations, and to ameliorate the increase of tumor metastases induced by surgical stress in this model (Franchi et al., 2007). Although these are only preclinical data from an animal model of lung colonization by tumor cells injected intravenously, these findings suggest that an adequate treatment of surgical stress-induced immunosuppression with an opioid like buprenorphine, which is devoid of immunosuppressive effects in animal experiments, may also play a protective role against the metastatic diffusion following cancer surgery in patients. This seems to be particularly relevant for some breast, neck, lung and colorectal cancers for which the presence of low NK activity is predictive of poor outcome (Fujisawa and Yamaguchi, 1997).

2.2. Pharmacokinetics

2.2.1. Absorption, distribution, metabolism and elimination

The general pharmacokinetics of buprenorphine have been extensively reviewed (Heel et al., 1979) and will not be described in detail here. Following parenteral administration, buprenorphine plasma concentrations rapidly reach peak levels (2–5 min after injection). The elimination of buprenorphine is divided into a fast and slow phase. Following parenteral administration, the elimination half-lives are 2 min (fast) and 2–3 h (slow) (Bullingham et al., 1980). After sublingual buprenorphine, peak blood levels were found 2 h after a single dose followed by a rapid decline until 6 h (fast), and a gradual decline over more than 24 h (slow) (Bullingham et al., 1980). The absolute bioavailability of sublingual buprenorphine is estimated to be approximately 50–60% (Mendelson et al., 1997; Nath et al., 1999). Buprenorphine shows 96% plasma protein binding (Heel et al., 1979). The pharmacokinetic characteristics of transdermal buprenorphine will be discussed later in this review.

Approximately two-thirds of a buprenorphine dose is excreted unchanged, whilst the remaining third is predominantly metabolised in the liver (but also in the gut wall) by glucuronidation to buprenorphine 3-glucuronide, and by *N*-dealkylation via the major hepatic enzyme system cytochrome P450 3A4 (CYP3A4), yielding the metabolite norbuprenorphine (Heel et al., 1979; Cone et al., 1984). Norbuprenorphine is found in human plasma after repeated administration of buprenorphine and is excreted in the urine after subsequent conjugation. Norbuprenorphine is about 40 times less analgesic than its parent drug, whereas buprenorphine 3-glucuronide and the other conjugated metabolites are completely inactive (McQuay et al., 1986). There is evidence of enterohepatic recirculation with biliary excretion of buprenorphine glucuronide, and hydrolysis in the lower gastrointestinal tract (Brewster et al., 1981).

In patients with severe chronic liver disease such as cirrhosis, CYP3A4 activity may be significantly reduced, and metabolism and clearance of buprenorphine may be altered (McQuay et al., 1986; Tegeder et al., 1999). Since in liver cirrhosis, however, glucuronidation is thought to be less altered compared to hepatic oxidation capacity, the transformation and elimination of buprenorphine should be less affected. Nevertheless, the sensitivity to buprenorphine may increase in parallel to the decline in liver function, changing both the duration and intensity of action. Of course, other drugs or interventions that influence hepatic blood flow or enzyme activity may also change buprenorphine clearance. Thus, patients with severe hepatic impairment should be closely monitored during treatment with buprenorphine, and lower initial doses and careful titration is advisable (Kress, 2005), but hepatic impairment seems to have only minor, if any effects on the clinical action, pharmacology and clearance of buprenorphine (Tegeder et al., 1999).

As buprenorphine is mainly (80–90%) excreted by the biliary system and enterohepatic recirculation (Brewster et al., 1981; Heel et al., 1979), its elimination is not affected by impaired renal function (Filitz et al., 2006). Thus, normal doses can be given in patients with renal dysfunction (Böger, 2006; Filitz et al., 2006; Hand et al., 1990), and buprenorphine pharmacokinetics are not altered with advanced age when renal impairment is common (Hand et al., 1990; Mühlberg and Platt, 1999). Therefore, buprenorphine is a suitable and safe treatment option in elderly patients and those with severe renal insufficiency (Kress, 2005), including those requiring haemodialysis (Filitz et al., 2006).

2.2.2. Drug interactions

Although buprenorphine and its major metabolites are inhibitors of CYP2D6 and CYP3A4 (Iribarne, 1997), no clinically relevant interactions with other drugs metabolised by the P450 system are to be expected at therapeutic concentrations (Zhang et al., 2003). *In vitro* experiments in human liver microsomes did not show major interactions with other CYP-metabolised drugs, because the clinical drug concentrations reached are below those concentrations needed for a 50% inhibition, which are 2000 times higher than the therapeutic plasma levels (Umehara et al., 2002). Nevertheless, care should be taken when buprenorphine is coadministered with monoamine oxidase inhibitors and other drugs affecting CYP3A4.

Pharmacological agents that interfere with CYP3A4, such as erythromycin, ketoconazole, and HIV protease inhibitors could theoretically decrease the production of norbuprenorphine. Drugs that induce CYP3A4 activity, such as phenobarbitone, carbamazepine or phenytoin could increase buprenorphine levels. As the metabolism of certain benzodiazepines also involves CYP3A4, excessive CNS depression due to the combination of buprenorphine and benzodiazepine may occur in patients with impaired liver function. The clinical relevance of these CYP3A4 interactions remains unclear and speculative for doses used in analgesic treatment (Bridge et al., 2003; Chiang and Hawks, 2003), however, recent reports from France on deaths involving buprenorphine overdose coadministered with benzodiazepines by opioid abusers might also partly reflect such benzodiazepine–buprenorphine interactions at extremely high doses in individuals with toxically or infectiously compromised liver function (Kintz, 2001).

Although 96% of buprenorphine is bound to plasma proteins, no relevant competition for transport proteins occurs in the plasma, as buprenorphine primarily binds to α- or β-globulins and not to albumin like most other drugs (Heel et al., 1979). As with other opioids, there are always interactions between buprenorphine and other CNS-depressant drugs, such as benzodiazepines. Excessive CNS depression is probably due to additive or synergistic pharmacodynamic effects unrelated to hepatic metabolism and pharmacokinetics.

2.2.3. Transdermal route

A transdermal patch formulation of buprenorphine with three different patch strengths: 35, 52.5 and 70 μg/h (Transtec®) is widely available across Europe. Each matrix patch continuously delivers buprenorphine for up to 96 h (4 days) across the skin and into the systemic circulation, corresponding to 0.8, 1.2 and 1.6 mg/day for the 35, 52.5 and 70 μg/h patch strengths, respectively (Fig. 5). The release of buprenorphine from the matrix system is regulated mainly by the concentration gradient across the skin and patch (Sittl, 2005). Recently, a second transdermal buprenorphine patch has been introduced in the UK, Germany and some other countries (Norspan®, Butrans®). This low-dose patch comes in patch strengths of 5, 10 and 20 μg/h released for 7 days to treat chronic pain after failure of non-opioid analgesics (Johnson et al., 2005). This low-dose form will not be discussed in more detail as no published data are available so far.

An open-label, three-way crossover study in 24 healthy volunteers evaluated the single-dose pharmacokinetics of transdermal buprenorphine 35 μg/h and 70 μg/h (Terlinden and Stadler, 2000). With the first application to the skin, plasma concentrations of buprenorphine increased steadily with time, and the minimum effective therapeutic dose (100 pg/ml) was reached at some 21 h and 11 h following the application of a single 35 and 70 μg/h patch, respectively (Table 1, Terlinden and Stadler, 2000). After about 60 h, peak plasma concentrations (C_{max}) of 305 and 624 pg/ml were reached for the 35 and 70 μg/h strength patch, respectively.

Table 1
Pharmacokinetic parameters of transdermal buprenorphine (Terlinden and Stadler, 2000)

Parameter	Transdermal buprenorphine dose	
	35 μg/h	75 μg/h
AUC (pg/h/ml)	20228 ± 9055	43040 ± 14041
t_{max} (h)	57 ± 15	59 ± 16
c_{max} (pg/ml)	305 ± 117	624 ± 185
MRT (h)	67 ± 5	67 ± 6
t (h)	21 ± 16	11 ± 6
dt (h)	71 ± 27	108 ± 19
$t_{1/2}$	25.3 ± 9.6	27.4 ± 7.0

With repetitive patch administrations, buprenorphine plasma concentrations increase, and steady state levels are normally reached after the third consecutive patch application (Evans and Easthope, 2003). In an open, randomised, parallel-group multiple-dose pharmacokinetic study of buprenorphine (Grünenthal data on file), the minimum effective concentration (100 pg/ml) was reached after 31, 14 and 13 h, respectively, with the 35, 52.5 and 70 μg/h patches. Over the total 216 h observation period, constant and comparable delivery of buprenorphine was observed, with mean C_{max} values ranging from 263.0 to 379.4 pg/ml, 332.1 to 528.7 pg/ml, and 390.1 to 578.2 pg/ml for the 35, 52.5 and 70 μg/h patches, respectively. A less pronounced increase in the area under the curve (AUC) values from the second to third patch application indicated the transition to steady state.

Transdermal buprenorphine is characterised by a bioavailability of approximately 50% (Evans and Easthope, 2003), which is comparable to sublingual buprenorphine (~55%) (McQuay et al., 1986). As should be expected, no differences in the pharmacokinetics of transdermal buprenorphine in patients with or without renal insufficiency could be seen (Hand et al., 1990; Filitz et al., 2006), and transdermal buprenorphine pharmacokinetics were unaffected in elderly patients (Likar et al., 2005).

3. Clinical efficacy in chronic pain

3.1. Cancer-related pain

In general, high-grade controlled clinical trials focusing exclusively on cancer pain patients are still lacking with buprenorphine. Nevertheless, the analgesic efficacy of transdermal buprenorphine

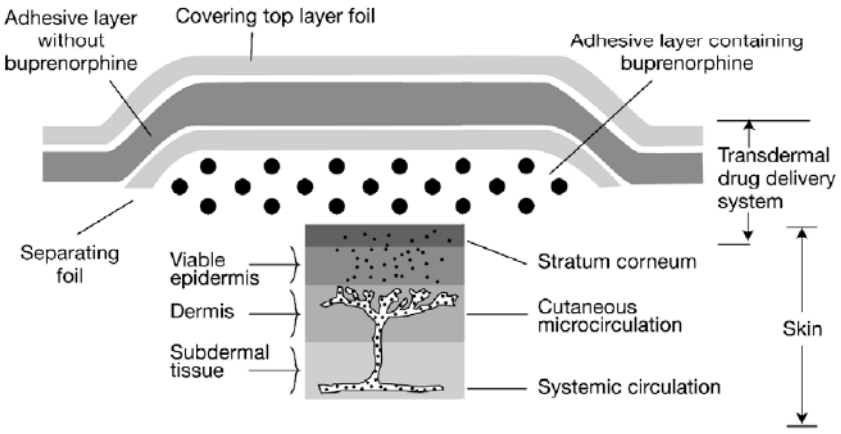

Fig. 5. The Transtec® matrix system (adapted from Evans and Easthope, 2003).

in cancer-related pain has been demonstrated in a number of placebo-controlled studies of mixed patient populations. Three early studies have confirmed the analgesic efficacy and safety of transdermal buprenorphine in patients with chronic cancer and non-cancer pain (Böhme and Likar, 2003; Sittl et al., 2003; Sorge and Sittl, 2004). A recent report, published as an abstract only (Poulain et al., 2006), has focussed on the evaluation of the transdermal buprenorphine 70 μg/h-patch in patients with severe, chronic cancer pain. Following a run-in period, patients were randomised to receive transdermal buprenorphine (70 μg/h) or placebo. Sublingual buprenorphine (0.2 mg) was allowed to treat episodes of breakthrough pain. The primary efficacy outcome measure was the proportion of patients responding to treatment (defined as patients completing at least 12 days of the double-blind period, with an average pain intensity score of <5 on the numerical rating scale (NRS) during the last 6 days of treatment, and not using more than two tablets of rescue medication per day). Significantly more patients receiving transdermal buprenorphine 70 μg/h responded (74.5%), compared to placebo (50%, $P = 0.0003$). Pain intensity was significantly lower in the transdermal buprenorphine group (1.8) compared with placebo (3.0, Fig. 6). In addition, the daily consumption of sublingual tablets was 50% higher in the placebo-treated patients, compared with patients treated with transdermal buprenorphine.

The results from the placebo-controlled trials in mixed non-cancer and cancer pain populations were also confirmed by retrospective surveys (Radbruch, 2003; Radbruch et al., 2001), and post-marketing surveillance (PMS) studies reflecting daily practice: A large PMS study involving 13,179 patients (male and female, mean age 68.3 years) recruited from hospitals, outpatient clinics and GP practices across Germany was conducted to evaluate the efficacy and safety of transdermal buprenorphine in routine clinical practice over a 9 months period (Griessinger et al., 2005). Of the total number of patients, 28% ($n = 3690$) had moderate-to-severe chronic cancer pain. The most frequent cancer diagnoses were lower respiratory tract cancer (16%), urogenital (16%) and breast cancer (15%). Other additional analgesics (opioids or NSAIDs) were required in 53% of patients. The majority of patients (78%) were treated with transdermal buprenorphine 35 μg/h. Good or very good pain relief was achieved in 84% of cancer patients with transdermal buprenorphine, compared to only 6.2% under the previous treatment. At the end of the study, only 4% of cancer patients reported poor or no pain relief. Eighty percent of cancer patients did not need a change of patch strength; two thirds of these reported very good and good pain relief.

An open PMS study conducted in Spain enrolled 1223 patients (male and female, mean age 64.6 years), 207 (18%) of whom had recorded chronic moderate-to-severe cancer pain that had not responded to non-opioid analgesics (Muriel et al., 2005). Transdermal buprenorphine 35 μg/h was used to treat the majority of patients (89%). After 3 months, the 35 μg/h patch was still being used by 52% of patients, and they were satisfied with the pain relief provided. Pain relief was reported as very good or good in 89% of patients, increasing from 5% prior to the start of the study.

Another open, multicentre, retrospective, pharmaco-epidemiological study was performed using data collected from 164 patients (average age 64.3 ± 12 years) with moderate-to-severe cancer pain attending pain centres throughout Spain (Muriel, 2004). The majority of patients continued with low doses of transdermal buprenorphine (35 or 52.5 μg/h) until the end of the study. At baseline 84% of patients reported a pain score of 7. After 2 weeks, 41% of patients reported a pain score of <4, rising to 76% after 8 weeks.

In an open, randomised, prospective study in 52 cancer patients with chronic pain over at least 1 year, transdermal buprenorphine 35μg/h was compared to oral SR morphine 60 mg/d (Pace et al., 2007) during a study period of 8 weeks. In both treatment groups, oral tramadol (up to 200 mg/d) was provided as rescue medication. Patients treated with transdermal buprenorphine experienced significantly greater improvement in pain and quality of sleep as well as a positive effect on general quality of life compared to morphine. As the authors used an equipotency ratio of about 1:30 instead of the recently suggested ratio of 1:100 between buprenorphine and morphine, the dose of 35 μg/h buprenorphine should have been expected to provide superior analgesia compared to the actual dose of 60 mg/d morphine (which was in fact the case), but interestingly the observed intensity of adverse effects was lower in the buprenorphine versus the morphine group, requiring more frequent use of symptomatic drugs for vomiting and constipation in the latter. Thus, also this study not only confirmed the efficacy of buprenorphine in cancer patients, but also its benign profile of adverse reactions compared to oral morphine. The most compelling

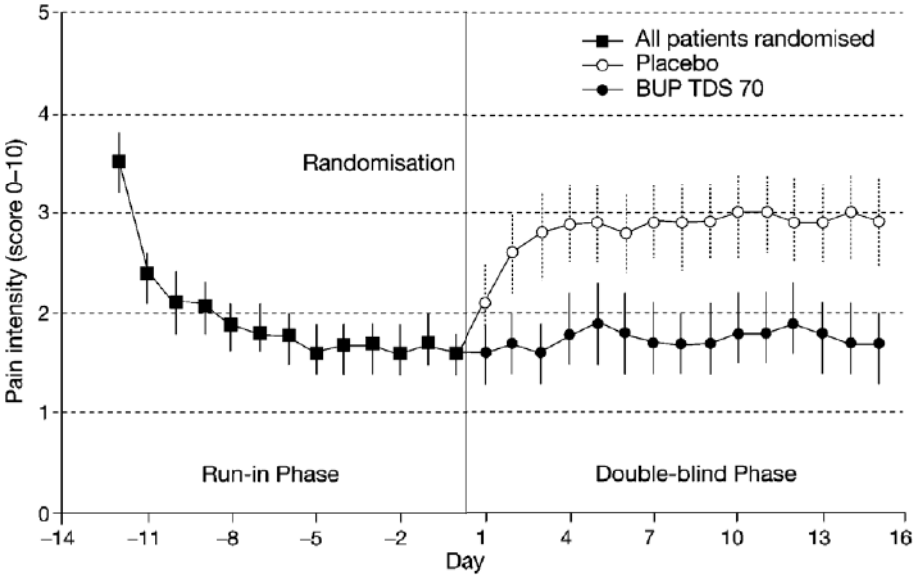

Fig. 6. Change in pain intensity in cancer-related pain (Poulain et al., 2006). *Key*: BUP TDS 70 = buprenorphine 70 μg/h-patch, three times daily.

evidence for the superior safety of buprenorphine is the near absence of lethal overdose cases in the literature attributable to a respiratory depression produced by buprenorphine alone (but see Kintz, 2001). There have been recent case reports of overdose deaths from France, where buprenorphine has been approved for treatment of opioid dependence since 1996, which suggest that the risk of respiratory depression from overdose is substantially increased in individuals with polysubstance abuse, particularly benzodiazepine abuse (Kintz, 2001).

Preliminary data from 10 cancer patients in an open study using the 70 μg/h patch (Mercadante et al., 2007) have contradicted the previous concerns about a ceiling effect in severe cancer pain by showing that the use of up to 140 μg/h doses of transdermal buprenorphine resulted in stable pain control for 6 out of these 10 patients. The other 4 patients not responding to 140 μg/h of transdermal buprenorphine required higher doses of other strong opioids suggesting that they were in need of a more rapid opioid escalation. The authors concluded that high doses of transdermal buprenorphine are effective for cancer pain management.

Finally, a published series of 3 case studies in patients with pain from renal and metastasising prostate and breast cancer further supports the effective use of transdermal buprenorphine in the long-term treatment of advanced cancer pain (Schriek, 2004).

3.2. Non-cancer pain

The analgesic efficacy of transdermal buprenorphine in non-cancer pain has been demonstrated in various studies, but apart from the aforementioned earlier placebo-controlled studies, where transdermal buprenorphine was shown to be effective and well tolerated in different non-cancer pain conditions (Böhme and Likar, 2003; Sittl et al., 2003; Sorge and Sittl, 2004), conformational results have been reported mainly from post-marketing surveillance. Thus, again, more data from randomised, controlled or comparative clinical studies would be desirable to further increase the strength of evidence.

Two open, retrospective, pharmaco-epidemiological studies conducted in Spain evaluated the use of transdermal buprenorphine, in conjunction with oral tramadol or morphine as rescue therapy, in chronic non-cancer pain of different aetiologies (Barutell, 2004; Gonzalez-Escalada, 2004). Patients (⩾18 years) with chronic pain were included in the two studies, if treatment with transdermal buprenorphine was indicated. Transdermal buprenorphine provided effective analgesia over the respective 6 or 8 week observation periods. Mean VAS scores (±SD) at baseline were 7.7 (±1.3) (Barutell, 2004) and 7.8 (±1.3) (Gonzalez-Escalada, 2004), compared to 3.6 (±1.6) and 3.7 (±1.9), respectively, at the final assessment. The analgesic efficacy of transdermal buprenorphine was rated by the physicians as good or very good in >70% of patients. Transdermal buprenorphine 35 μg/h was most frequently used. Significantly, only 50% of patients required tramadol rescue therapy over the course of the study (Barutell, 2004).

A third, open, retrospective, pharmaco-epidemiological study also from Spain evaluated data from 361 patients (mean age 60.6 years) with chronic nociceptive pain treated with transdermal buprenorphine (Camba, 2004). The majority (61.4%) of patients were suffering from osteoarticular pain. In 95.6% of these patients another previous pharmacological pain treatment had already failed. The primary efficacy measure, pain intensity, was assessed over an 8-week period, using the VAS and the Lattinen index. Transdermal buprenorphine reduced the average pain intensity by more than 50% over the entire treatment period. The VAS score decreased from 7.7 at baseline to 3.4 at week 8. The mean Lattinen index was reduced from 12.7 to 6.2.

In a German post-marketing surveillance study, 72% (9489) of patients treated with transdermal buprenorphine had non-cancer pain (Griessinger et al., 2005). Of these patients, 77% suffered from musculoskeletal pain and 23% from neuropathic pain. Most patients (96%) had already received analgesic therapy before the start of transdermal buprenorphine treatment. Fifty-six percent of these patients had experienced no or little pain relief under the previous treatment. The majority (81%) of patients received the transdermal buprenorphine 35 μg/h patch. At the end of the study, 79% of patients rated their pain relief as very good or good, and 51% of patients did not require any concomitant analgesic medication.

In a Spanish post-marketing surveillance study pain was mostly musculoskeletal in 968 patients diagnosed with non-cancer pain (Muriel et al., 2005). In total, 94% of patients started on transdermal buprenorphine 35 μg/h, and after 3 months 82% of patients were satisfied with the pain relief provided by this patch strength. Transdermal buprenorphine increased the proportion of patients reporting very good or good pain relief from 4% before treatment to 85% at the end of the study.

3.2.1. Neuropathic pain

Recent animal and human experimental studies have shown that buprenorphine appears to dampen central sensitisation suggesting its potential efficacy in neuropathic pain (Christoph et al., 2005; McCormack et al., 1998; Koppert et al., 2005). Buprenorphine was effective in the formalin test in neonatal and adult rats, with superior efficacy in neonatal rats indicating greater antineuropathic potential compared to other opioids (Hans, 2007). The dose-dependent analgesic profile of buprenorphine was confirmed in several neuropathic pain models, including peripheral nerve (e.g. sciatic nerve) and spinal cord injury pain, chronic sciatic nerve constriction model, spinal nerve ligation, chemically (streptozocine and vincristine) induced polyneuropathic models, and pertussis toxin-induced experimental neuropathy (Hans, 2007; Christoph et al., 2005).

In a double-blind, randomised, controlled dose–response study, long-term neuropathic pain after thoracotomy was adequately controlled with intravenous buprenorphine (Benedetti et al., 1998). No randomized controlled clinical trials for the treatment of neuropathic pain, however, can be found for transdermal buprenorphine. This fact limits—of course—the strength of evidence for the successful use of buprenorphine in this indication and clearly signals the need for further studies in this domain. In general, clinical data on the management of neuropathic pain with opioids are sparse, and head-to-head comparisons of buprenorphine with other strong opioids in this indication are sorely missing. Nevertheless, there exist clinical data from open studies and case reports with transdermal buprenorphine which show that it is also effective in patients reporting neuropathic pain (Rodriguez-Lopez, 2004; Griessinger et al., 2005). An open, multicentre, retrospective study has analysed data from 237 patients who reported various neuropathic pain syndromes (lumbosciatica 30%, pain syndrome following failed shoulder surgery 13%, and post-herpetic neuralgia 12%) (Rodriguez-Lopez, 2004). Patients were treated with transdermal buprenorphine over an 8 week period, with 70% of patients receiving the 35 μg/h patch strength. Mean pain score (VAS) decreased by 55% over the 8 week period. The pain score progressively declined from 7.7 to 5.1 after 2 weeks, to 3.9 after 4 weeks, and to 3.5 after 8 weeks. Furthermore, Likar and Sittl (2005; Likar et al., 2003) have published case studies demonstrating the successful treatment of resistant, complex neuropathic pain with transdermal buprenorphine. The data reviewed there are promising, but nevertheless, at least a controlled randomised study confirming the efficacy of transdermal buprenorphine in a large sample of patients suffering from typical chronic neuropathic pain is still required, before any definite conclusion on the efficacy of buprenorphine in chronic neuropathic pain should be drawn.

3.3. Long-term clinical use

An open-label, long-term follow-up study (up to 5.7 years) analysed 1760 patient-months of experience with the buprenorphine 35 μg/h patch in 239 patients, who had participated in one of the 3 previous double-blind, placebo-controlled studies evaluating the short-term efficacy and safety of the patch (Böhme and Likar, 2003; Sittl et al., 2003; Sorge and Sittl, 2004). Forty-two (17.6%) patients continued therapy for at least 12 months, 37 (15.5%) of them for >12 months. The maximum follow-up period was 3.4 years in cancer and 5.7 years in non-cancer patients. The majority (65.9%) of patients managed their pain with the patch alone or took not more than 1 additional sublingual tablet daily for breakthrough pain. At least satisfactory pain relief was reported by 215 (90.0%) patients. The most common systemic adverse drug reactions were nausea (9.2%), dizziness (4.6%), vomiting (4.2%), constipation (3.8%), and tiredness (2.9%), whereas the most common local adverse drug reactions were erythema (12.1%), pruritus (10.5%), and exanthema (8.8%) (Likar et al., 2006).

3.4. Combination with other μ-opioids

In contrast to previous concerns based on preclinical animal data, a number of clinical and post-marketing surveillance studies have clearly shown that buprenorphine can be safely and effectively combined with full μ-agonists thereby providing an additive analgesic effect. These clinical results confirmed the already above mentioned more recent experimental studies, which have clearly shown that, at clinically relevant doses, buprenorphine acts like a full μ-opioid receptor agonist (Cowan et al., 2005; Kögel et al., 2005). In one non-interventional trial, 93 patients with chronic pain on transdermal buprenorphine were more successfully treated with a combination of buprenorphine and immediate-release (IR) morphine (Gonzalez-Escalada, 2004). In another study of similar design, 297 patients with chronic pain were treated with transdermal buprenorphine, and tramadol was given in addition for breakthrough pain. This combination proved effective and buprenorphine was compatible with the full μ-agonist tramadol (Barutell, 2004). The compatibility of buprenorphine with full μ-agonists has been further confirmed by a recent open-label study evaluating the effectiveness and safety of intravenous morphine for the treatment of episodic/breakthrough pain in 29 patients with advanced cancer who received transdermal buprenorphine (Mercadante et al., 2006). A total of 98 of the 106 episodes in the 29 patients were successfully treated with intravenous morphine (33% reduction in pain intensity within 15 min). No clinically relevant adverse events were reported.

In addition, it has been shown that switching from buprenorphine to another opioid and *vice versa* provides effective pain relief based on equianalgesic doses (Atkinson et al., 1990). These clinical observations are in line with recent preclinical data, demonstrating that administration of morphine after the decline of the acute buprenorphine effect has an additive—rather than an antagonistic—effect, with full analgesic efficacy (Kögel et al., 2005). Importantly, this was independent of the order of opioid administration.

4. Safety and tolerability

The reported incidence of adverse events is low with most being transient and mild-to-moderate in severity (Likar, 2006). In early placebo-controlled trials, the overall incidence of adverse events ranged between 23% and 78.8% with no significant differences between any of the treatment groups or placebo (Böhme and Likar, 2003; Evans and Easthope, 2003; Sorge and Sittl, 2004). Few patients treated with transdermal buprenorphine withdrew from the studies because of adverse events. In one Phase III study, 17 patients (10.8%) withdrew due to serious or severe adverse events during the treatment period (Sittl et al., 2003). The most frequently reported adverse events (occurring in >5% of patients taking Transtec®) from an analysis of the pooled data of the randomised, placebo-controlled studies are shown in Fig. 7 (Evans and Easthope, 2003).

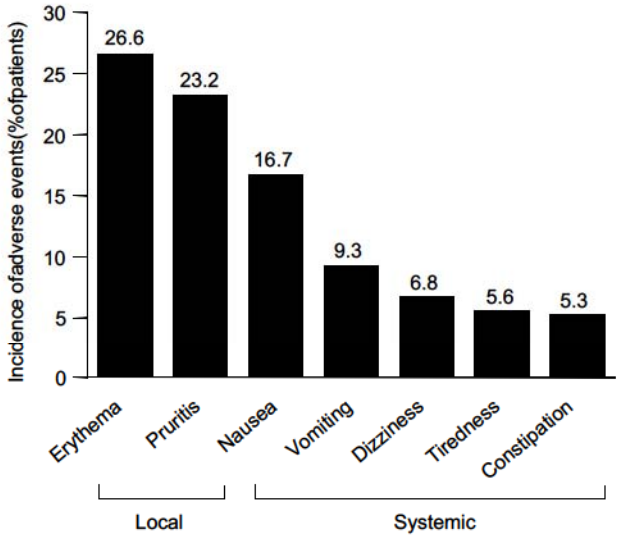

Fig. 7. Adverse events occurring in >5% patients taking Transtec® during the three, randomised phase III trials (pooled data) (Evans and Easthope, 2003).

4.1. Systemic adverse events

Systemic adverse events occurred in 38%, 50% and 44% of patients receiving 35, 52.5 and 70 μg/h transdermal buprenorphine, respectively, compared to 38% in placebo patients in the three randomised phase III studies (Evans and Easthope, 2003). In total, systemic adverse events (typical opioid effects, most affecting the gastrointestinal tract and the CNS) were attributed to buprenorphine treatment in 63% of patients (Evans and Easthope, 2003). These pooled data from the randomised trials showed that patients receiving 35 μg/h transdermal buprenorphine experienced the same incidence of systemic side effects as placebo (38% versus 37.8%, respectively, Evans and Easthope, 2003). With the 52.5 and 70 μg/h patch strengths, the proportion of patients suffering from systemic adverse events increased slightly to 50% and 44%, respectively. In the long-term study, systemic events were reported by 45.5% of patients, but only 20% were associated with the study medication (Likar et al., 2006).

4.2. CNS events

Like other opioids, buprenorphine may cause CNS effects including nausea. The previously mentioned pooled analysis of the randomised Phase III studies, however, showed no statistically significant differences in the incidence of the most common CNS events (nausea, dizziness and tiredness) between patients treated with transdermal buprenorphine and those treated with placebo (Evans and Easthope, 2003). Furthermore, patients receiving long-term transdermal buprenorphine had a lower incidence of CNS adverse effects (Likar et al., 2006). During the post-marketing surveillance of transdermal buprenorphine, nausea was reported in only 4% of patients and vomiting in 1.6% (Griessinger et al., 2005). This indicates that the overall incidence of reported systemic

events might be lower in clinical practice than in clinical studies, which is in fact no surprise. Interestingly, transdermal buprenorphine also seemed to produce a lower incidence of CNS events than other opioids including transdermal fentanyl (Shipton, 2005; Griessinger et al., 2005; Radbruch et al., 2001; Radbruch, 2003). Recently, the low potential for CNS events was underlined by a Danish register-based study exploring the relationship between fractures during the year 2000 and the use of opioids (Vestergaard et al., 2006). The use of morphine, fentanyl, oxycodone or methadone was found to correlate with an increased overall fracture risk, which may be explained by the increased risk of falls due to CNS effects (such as dizziness) associated with opioid use. Buprenorphine was the only strong opioid whose use did not correlate with an increased fracture risk. However, this is only indirect evidence, and prospective, randomized head-to-head comparisons between the respective opioids and buprenorphine are necessary.

4.3. Constipation

Although constipation was reported in 5.3% of patients using transdermal buprenorphine during clinical trials (Likar et al., 2003), post-marketing surveillance revealed a much lower incidence, with less than 1% of patients experiencing constipation (Griessinger et al., 2005). A sub-analysis of patients >60 years did not find an increased rate of constipation (1.1%) in the elderly, thus supporting the previous findings (Nasar et al., 1986). This is important as elderly patients are at particularly high risk of constipation (Shipton, 2005).

Buprenorphine has been shown to have a lower rate of constipation than morphine or fentanyl (Shipton, 2005). One study found that constipation occurred in 1.2% of patients receiving buprenorphine, compared to 6.7% taking morphine (Bach et al., 1991). Another PMS study evaluating the effect of transdermal fentanyl in cancer pain found that the incidence of constipation was 4% (Radbruch et al., 2001), suggesting that the risk of constipation is lower with transdermal buprenorphine than with transdermal fentanyl (1% *versus* 4%) (Griessinger et al., 2005; Radbruch, 2003). Compared to oral morphine, transdermal administration seems to offer generally improved gastrointestinal tolerability, as opioid receptors in the gut wall are not directly targeted (Shipton, 2005).

4.4. Local skin reactions

In the original clinical study program, local skin reactions were assessed at patch removal, and occurred in about a third of patients, irrespective of whether they contained buprenorphine or placebo (Evans and Easthope, 2003). These local reactions most probably resulted from patch removal due to the adhesive material rather than being directly related to buprenorphine. The most frequent local reactions were erythema (26.6%) and pruritus (23.2%), which were generally mild-to-moderate and transient in nature (Fig. 7) (Evans and Easthope, 2003). In the long-term follow-up study the incidence of local reactions was lower (erythema 11.3% and pruritus 9.2%) (Likar, 2006; Likar et al., 2006). Furthermore, the data from the German PMS study suggest that local skin reactions occur much less frequently in routine clinical practice (contact dermatitis 0.8%, and pruritus 0.7%) (Griessinger et al., 2005).

4.5. Dosage in elderly and patients at risk

As discussed earlier, the pharmacokinetics of buprenorphine are not altered in patients with renal impairment (Böger, 2006; Hand et al., 1990; Filitz et al., 2006) or in elderly patients (Kress, 2005; Likar et al., 2005). Findings from the German PMS study suggest comparable tolerability for transdermal buprenorphine in elderly and young patients, with the frequency of adverse reactions being even lower in patients >70 years old (Griessinger et al., 2005). Transdermal buprenorphine was safely used in the elderly as well as in patients with reduced renal function, renal insufficiency and those with end-stage renal disease requiring haemodialysis, without the need for dose adjustment or special adverse event monitoring. Patients with hepatic impairment should be monitored, as buprenorphine metabolism may be affected (Kress, 2005), as should patients with a fever, since changes in skin permeability may affect buprenorphine absorption. Transdermal buprenorphine is contraindicated in patients with severe respiratory depression, opioid dependence, myasthenia gravis or delirium tremens, and those who are breast-feeding or pregnant. Furthermore, transdermal buprenorphine is not approved for individuals $\leqslant$18 years old.

Data from clinical practice show that it is possible to increase the dose above the currently recommended maximum with good pain relief even in severe cancer pain and without tolerability problems (Menten et al., 2006). For initial titration or down-titration, it is possible to provide smaller doses of transdermal buprenorphine, by cutting the patch in half (Louis, 2006). For patients pre-treated with other opioids, equipotency considerations need to be taken into account to apply the correct dose. Recent evidence from a cohort study suggests that the equipotency ratio of transdermal buprenorphine to morphine is 1:110 to 1:115 (Likar et al., 2008; Sittl et al., 2005). When a 1:100 equipotency ratio of transdermal fentanyl to oral morphine is assumed, this results in equipotent doses of 75 μg/h for transdermal fentanyl and 70 μg/h for transdermal buprenorphine (Sittl et al., 2005).

5. Conclusion

Buprenorphine acts both as a partial μ-opioid receptor agonist and a κ-opioid receptor antagonist. After binding to μ-opioid receptors with high affinity, it slowly dissociates, resulting in a slow onset and long duration of analgesic action. Despite past misconceptions concerning its analgesic potency, buprenorphine, in fact, has been shown to have a dose–linear response curve, with no analgesic 'ceiling effect' observed within the therapeutic analgesic dose range in man. Interestingly, buprenorphine also seems to produce a long-lasting antihyperalgesic effect under certain conditions that is thought to result, at least in part, from its antagonism at the κ-receptor. Compared with full μ-opioid receptor agonists, such as morphine and fentanyl, buprenorphine has a lower risk of respiratory depression, withdrawal symptoms appear to be milder, and the risk of drug dependence and analgesic tolerance might be lower. Particularly when compared to transdermal fentanyl, buprenorphine offers several advantages: It shows little analgesic cross-tolerance to other opioids (Davis, 2005), and—within the therapeutic dose range—buprenorphine, unlike fentanyl, shows a ceiling effect for respiratory depression, but not for analgesia. For fentanyl, on the other hand, the analgesic efficacy has been shown to be dose-linear in a much wider range than it has been clinically proven for buprenorphine so far. In human pain models, the antihyperalgesia/analgesia ratio of buprenorphine is distinctly different from that of fentanyl, and, because of its more pronounced antihyperalgesic effect, buprenorphine may even prevent opioid-induced hyperalgesia. Finally, buprenorphine is safe in renal insufficiency and does not need any dose adaption even in end-state renal failure requiring haemodialysis. In general, however, the evidence supporting the promising reports on efficacy and tolerability of this drug is still limited with respect to available high-grade randomised control trials in defined patient groups (e.g. neuropathic pain, cancer pain, renal failure, patients requiring high opioid doses, etc.). Buprenorphine can be safely coadministered with full μ-agonists, and switching to buprenorphine from another opioid has been shown to be easily possible and to provide

effective pain relief. Furthermore, the risk of clinically relevant interactions with drugs metabolised by the CYP450 system seems relatively low under normal conditions.

The transdermal patch formulation of buprenorphine continuously releases buprenorphine for up to 4 days. It is indicated for use in moderate-to-severe cancer pain, and severe non-cancer pain not sufficiently responding to non-opioid analgesics. It has been shown to be effective for a broad range of chronic pain indications, including mainly nociceptive but also certain neuropathic pain conditions, although the strength of evidence is insufficient in the latter. Importantly, the pharmacokinetic profile of transdermal buprenorphine is not altered by advanced age or renal dysfunction, allowing its safe use, without dose adjustments, in elderly patients and those with renal impairment. Clinical trials, retrospective studies, and large-scale PMS studies in cancer and non-cancer patients showed a favourable safety profile which is typically opioid in nature. In conclusion, transdermal buprenorphine can be regarded as a now established and effective option in the treatment of chronic cancer and non-cancer pain.

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