ORIGINAL RESEARCH

Buprenorphine and pain treatment in pediatric patients: an update

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Introduction: The usual management of moderate to severe pain is based on the use of opioids. Buprenorphine (BPN) is an opioid with an analgesic potency 50 times greater than that of morphine. It is widely used in various pain models and has demonstrated efficacy and safety in adult patients; however, there are insufficient clinical trials in pediatric populations.

Purpose: The aim of this study was to perform an updated meta-analysis on the implementation of BPN in the treatment of pain in the pediatric population.

Methods: A bibliographic search was carried out in different biomedical databases to identify scientific papers and clinical trials with evidence of BPN use in children and adolescents.

Results: A total of 89 articles were found, of which 66 were selected. Analysis of these items revealed additional sources, and the final review included a total of 112 publications.

Conclusion: Few studies were found regarding the efficacy and safety of BPN use in children. In recent years, the use of this drug in the pediatric population has become widespread, so it is imperative to perform clinical trials and pharmacological and pharmacovigilance studies, which will allow researchers to develop dosage schemes based on the evidence and minimize the risk of adverse effects.

Keywords: buprenorphine, opioid, analgesia, child, adverse effects, pharmacokinetics

Introduction

Optimal pain treatment requires multimodal strategies based on the identification of the causal mechanisms and intensity to individualize treatment. Pain is defined as "an unpleasant sensory and emotional experience associated with real or potential tissue damage."[1,2]

Pain is the most common health symptom during childhood and adolescence.[3] Although the magnitude of the detrimental effects pain can have on a child is known, it is often inadequately evaluated and treated[4,5] due to ignorance of the pathophysiological aspects of pain at this stage of life and limited clinical information on the use of certain drugs.[6–8]

Pain can be classified into acute and chronic pain. The former is defined as the expected normal physiological response to adverse chemical, mechanical, or thermal stimuli associated with surgery, trauma, or acute diseases.[9] Over 80% of adult patients undergoing surgical procedures experience acute postoperative pain of moderate to severe intensity (75% of cases).[10] In children, the prevalence of postoperative pain is reported in up to 50% of cases[11] of which up to 20% develop postsurgical chronic pain.[12] Chronic pain can be caused by a variety of conditions. Chronic pain is the main

symptom experienced by children with cancer and occurs in at least 89% of patients in advanced stages of this disease.[13,14]

Analgesic therapy established by the World Health Organization (WHO) aims to keep pediatric patients calm and free of pain and provides pharmacotherapeutic strategies based on their intensity and pathologic condition.[15–17] The recommendation for the use of analgesics is as follows:

1. non-opioid analgesics (paracetamol and anti-inflammatory drugs);
2. opioids (morphine, methadone, hydromorphone, buprenorphine [BPN], fentanyl and oxycodone);
3. local anesthetics (lidocaine, bupivacaine and ropivacaine); and
4. adjuvant analgesics (anticonvulsants, antidepressants, corticosteroids and ketamine).

Opioids are an important tool for treating moderate to severe persistent pain. Approximately 60%–90% of children in palliative care will receive this type of medication.[18]

BPN is a semisynthetic opioid developed in the 1960s[19] and, although not the first line treatment for pain, has proven to be a good analgesic with prolonged effect.[20] In the 1980s, the US Food and Drug Administration authorized intravenous (IV) BPN administration, and subsequently other dosage forms were developed (Figure 1). In the 40 years of BPN use, there has been little information regarding its use and pharmacokinetics (PK) in children, especially in the treatment of chronic pain.

The aim of this study was to conduct an updated meta-analysis on the implementation of BPN in the treatment of pain in the pediatric population.

Methods

A search was performed on biomedical databases, The Cochrane Database of Systematic Reviews, EMBASE, MEDLINE (PubMed and Ovid), Scopus, KoreaMed, National Library of Australia, and LILACS, to identify articles concerning the use of BPN in children and adolescents. No time or language restrictions were applied.

The Medical Subject Headings terms used were as follows: BPN, pain, child, neonates, infant, adolescent, analgesia, pharmacokinetics, pharmacodynamics, adverse reaction, transdermal patch, sublingual, intravenous administration, and infusion intravenous.

The search in all databases yielded 89 results, duplicates and articles that after a critical reading were considered not relevant were eliminated, yielding 66 documents. From these sources, additional items were identified. The final review was performed with a total of 112 publications.

Pharmacological properties

BPN is a semisynthetic opioid derived from thebaine, with an antinociceptive effect 30–50 times more powerful than morphine.[27] In trials, intramuscularly administered BPN has 25 times more potency than intramuscular (IM) morphine and sublingual (SL) administration is 15 times more potent than IM morphine.[28]

BPN's chemical structure is basically that of an opioid with multiple chiral centers. However, a tert-butyl group in carbon position 7 contributes to its lipophilicity. BPN has a low molecular weight (467.64 g/mol) and is a base with a pKa between 8.2 and 10.0 and a melting point of 218°C.[27,29] BPN's physicochemical properties favor tissue penetration in both transdermal and transmucosal formulations.[29,30]

BPN is a centrally acting analgesic that binds to opioid receptors[19,31] to generate inhibition of the transmission of nociceptive impulses from the periphery to the spinal cord and activation of downstream pathways inhibitory modulating pain transmission. In addition, BPN can modify activity in the limbic system (affective and sensory-discriminative components).[32–34]
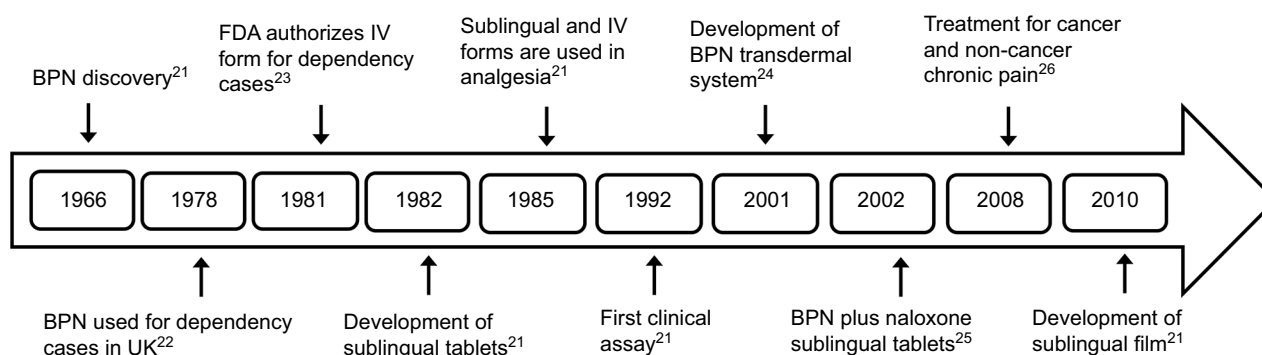

Figure 1 Timeline of development of pharmaceutical forms and authorized use of BPN.
Abbreviations: BPN, buprenorphine; FDA, US Food and Drug Administration; IV, intravenous.

BPN's pharmacological profile has not been fully resolved, since the union of BPN and the opioid receptor is high but not selective. Differences in the profile have been observed depending on the model (animal, human), conditions (in vitro/in vivo), and experimental model (pain, dependence, or respiratory depression). This finding has resulted in misconceptions that have limited the clinical utility in certain population groups.

Pharmacokinetics

Drug absorption is dependent on the route of administration and BPN can cross the blood–brain barrier and placenta. Parenteral administration generates brain concentrations 2–3 times greater than those achieved by oral administration. Some studies in rats indicate that BPN is rapidly distributed in the brain after IV administration. Due to its polarity, the metabolite norbuprenorphine rapidly penetrates the central nervous system (CNS) without modification.[23]

BPN has high affinity for globulins type α and β (95%–98%) and poor binding to albumin.[35] It possesses extensive first pass metabolism in the gut wall and the liver, primarily by cytochromes CYP3A4 and 3A5 (65%), CYP2C8 (30%), and with less active CYP2C9, CYP2C18, and CYP2C19. Cytochromes P450 (CYPs) transform BPN via N-dealkylation into norbuprenorphine (active metabolite). CYP3A4 may also catalyze hydroxylation of both compounds to generate hydroxybuprenorphine and hydroxynorbuprenorphine.[36] Moreover, the uridine diphosphate glucuronosyltransferases (UGT1A1 and UGT2B7) perform glucuronidation to obtain the inactive metabolites BPN-3-glucuronide and norbuprenorphine-3-glucuronide (Figure 2).[37] It is known that the maximum plasma norbuprenorphine concentrations are equal to or higher than BPN concentrations.
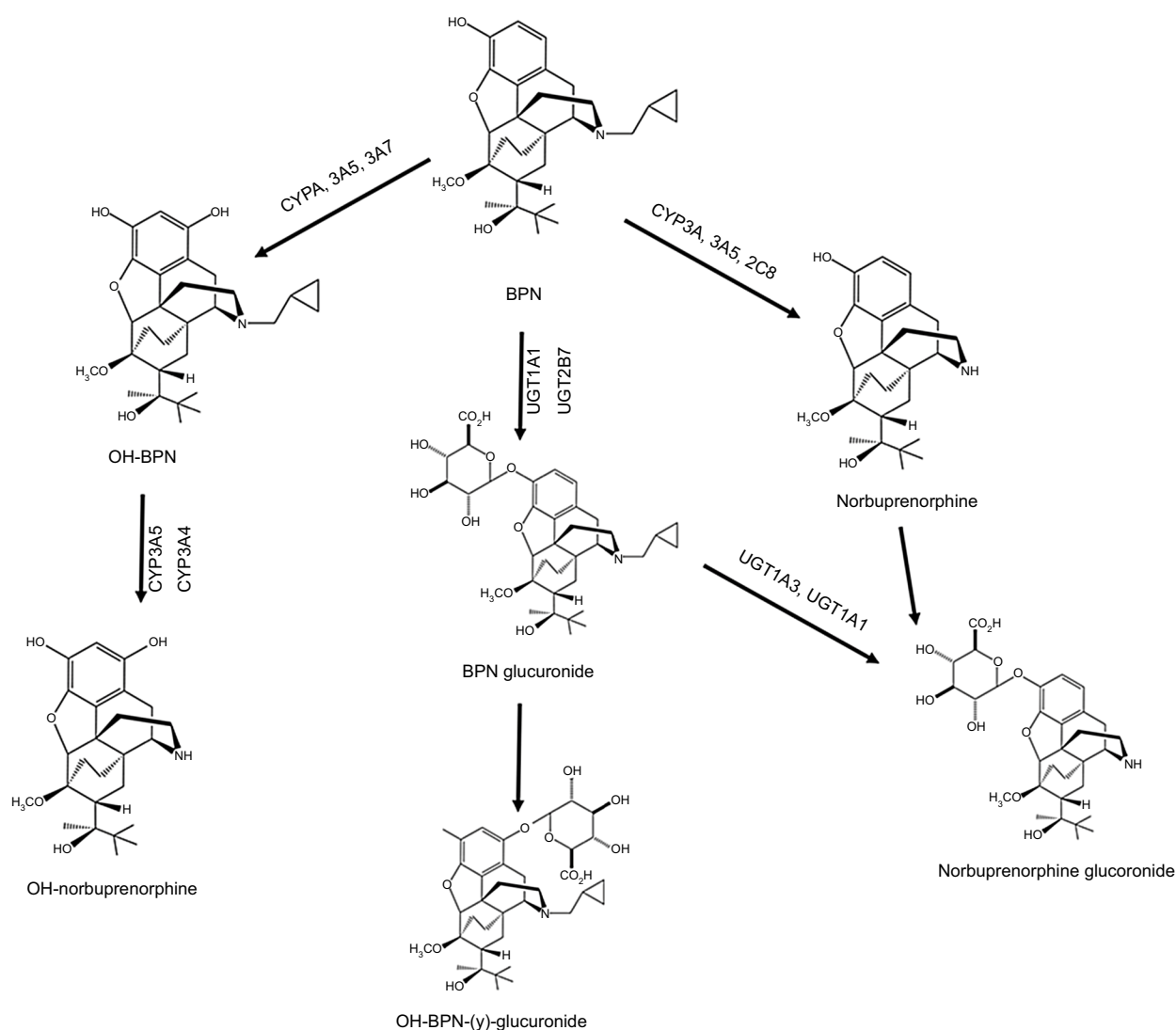

Figure 2 Metabolism of BPN. Cytochromes P450 produce hydroxybuprenorphine, hydroxynorbuprenorphine, and norbuprenorphine. The glucosyltransferases (UGT1A3, UGT1A1) produce BPN glucuronide, hydroxyl BPN glucuronide, and norbuprenorphine glucuronide.
Abbreviation: BPN, buprenorphine.

BPN is excreted in an unaltered or N-dealkylated form in the feces (50%–71%) and urine (10%–17%),[38] which favors its administration in patients with renal failure. This drug can be used in elderly patients because the PK is not affected by age.[39,40] It is also a safe opioid in patients with mild to moderate liver failure and does not require dosage adjustment.[41,42] The plasma elimination of BPN follows a multi-exponential curve with a half-life of ~3–5 hours in postoperative patients.[43] Its agonist and antagonist properties are related to the dosage and administration route.[41,44]

Pharmacokinetic parameters in adults

These values are dictated by the administration route as follows.

Intravenous

Absorption is immediate with 100% bioavailability. The maximum plasma concentration (Cmax) is reached in 2–5 minutes. Elimination has a rapid phase half-life ($t_{1/2}\alpha$) of 2–5 minutes, followed by a redistribution time ($t_{1/2}\beta$) of 20–30 minutes, and a slow phase time ($t_{1/2}\delta$) from 2 to 3 hours.[27,45]

Oral

Absorption is very low due to extensive first pass metabolism, with 10%–16% bioavailability. BPN tablets produce plasma levels of 50% compared to those achieved with liquid preparations.[46]

Sublingual

Absorption is rapid, with variable bioavailability of 30%–60% due to protein binding and interindividual variability. Cmax is reached at 2 hours. Plasma concentrations fall rapidly in the first 6 hours, then a gradual decrease is observed for 24 hours.[47,48] Tmax is variable in healthy volunteers; doses of 0.4 and 0.8 mg (drops) give Tmax values of 30 and 60 minutes, respectively. The same doses in sublingual tablets have Tmax values of 90 and 360 minutes, respectively.[23]

Transdermal

Distribution is rapid in nerve tissue, with 5% bioavailability.[49] The administration in patches containing 20 and 40 mg (release rate of 35 and 70 mg/h) shows that the minimum effective concentration (100 pg/mL) is reached at 21 and 11 hours after patch application, respectively.[50]

In another trial, the administration of a patch containing 20 mg (35 µg/h) achieved a Cmax of 300 pg/L and Tmax at 60 hours.[51] The area under the curve was 20.22 pg/h. No differences were observed in PK parameters in patients with renal failure nor were there parameter changes in older adults.[39,52,53]

Intranasal

The intranasal formulation is fast acting, with 50% bioavailability and a Tmax of 30 minutes.[23] Lipophilic drugs such as BPN are generally well absorbed from the nasal mucosa and have PK profiles such as those obtained by IV administration. This formulation is interesting for the treatment of irruptive cancer pain. The intranasal formulation is currently under development and has been used only in animal models and healthy volunteers.

Pharmacokinetic parameters in children

The PK of this drug has been described using a model of two or three compartments. In children, there is limited information regarding the estimation of PK parameters. The first study used allometric pediatric models to estimate parameters in children older than 2 years using the PK parameters of adult patients.[45]

In a 1989 study, BPN was administered intravenously at a premedication dose of 3 µg/kg among patients undergoing minor surgery (4.6–7.5 years). The PK showed a biexponential behavior (due to enterohepatic recirculation) with two half-lives, a quick half-life at 5 minutes and a slow half-life at 62 minutes. The mean clearance was 60 mL/min/kg and a volume of distribution at steady state was in the range of 1.2–8.3 L/kg. No correlation was found between the PK parameters and age, weight, or body surface area.[54] The average clearance is three times higher in children than adults; this is because the liver/body weight ratio is greater in children. The values of the volume of distribution at steady state were similar in both populations.[54] The author concluded that because the BPN clearance is higher in children than in adults, there are no contraindications for BPN use as an analgesic in children. A comparison of the PK values in adults and children is shown in Table 1.

In contrast, a study in preterm infants (27–32 weeks gestational age) receiving BPN at 0.72 µg/kg/h by continuous infusion concluded that this administration route does not provide stable sedation or analgesia and, therefore, its use is not recommended. Further, in this population the clearance is reduced due to the immaturity of glucuronidation systems.[55]

Pharmacodynamics

BPN is a partial mu receptor agonist, partial or complete opioid receptor-like 1 (ORL1) agonist, and kappa and delta receptors antagonist,[56–59] characterized by a lasting action

Table 1 Pharmacokinetic parameters in different pharmaceutical forms

Pharmacokinetic parameters	Pharmaceutical forms					
	Intravenous		Sublingual		Transdermal	
	Adults	Children	Adults	Children	Adults	Children
Bioavailability (%)	100	100	30–60[27,47,48]	30–55[27]		50[49]
C_{max} (ng/mL)	18.1±3.1[45]				300[51]	
T_{max} (min)	2–5[45]		30–180[27,47,48]	90–360[27]	3600[51]	660–1260[50]
$T_{1/2}$ (h)	3.06±0.6[45]	1.0±0.2[54]			25.3[51]	20±8[27]
Cl_T (mL/min·kg)	18.2±1.2[45]	60±19[54]	50[27]			0.14[27]
V_{ss} (L/kg)	2.7±0.5[45]	3.2±2[54]				6.2±2.1[27]

Note: Pharmacokinetic values obtained in clinical studies for adults and children.
Abbreviations: C_{max}, maximum plasmatic concentration; T_{max}, time to obtain C_{max}; $T_{1/2}$, half-life for buprenorphine; Cl_T, clearance total; V_{ss}, volume of distribution at steady state.

associated with a slow dissociation from the receptor and low intrinsic activity in in vitro assays.[38,60,61] These properties allow BPN to displace other mu-agonists and explain its therapeutic effect on opioid dependence. In contrast to the full mu receptor agonists, BPN has a pronounced anti-hyperalgesic effect[36] and does not cause internalization of opioid receptors which decreases the possibility of inducing tolerance or dependence.[29]

BPN is a potent opioid in low doses, but at higher doses it has a relative decreased potency, which is a feature of partial opioid agonists.[23] In adults, BPN has a ceiling effect on respiratory depression but not in analgesia.[38,61] The dose for the ceiling effect relates to the partial agonist activity of the receptors mu and ORL1.[62–65] It is thought that the supra-spinal component of the antinociception induced by BPN is not mediated by the opioid mu response, but by unique receptors.[41]

BPN's effects on ventilation are controversial. Hovell and Banks have reported that BPN has little effect on adult patients,[66,67] but other authors report ventilator depression as with morphine.[20,68] The magnitude of this respiratory effect is variable and independent of the interaction with the mu receptor.[69]

BPN ceiling effect in children is controversial and not well defined.[15] It is known that the opioid interaction with the mu receptor can depress respiration; this side effect is variable and dependent of different factors such as genetics, age, sex, concomitant medication, and others.[69] In fact, BPN and its active metabolite norbuprenorphine exhibit a respiratory depressant activity.

In previous studies performed by Dahan et al, they observed a nonlinear dose/response relationship, with a ceiling at above 0.1 mg/kg doses and a moderate increase of $PaCO_2$, providing lower rates of respiratory depression than other opioids, such as fentanyl;[70] further, they found that BPN's analgesic effect increased significantly using two different doses, while the respiratory depression was similar in magnitude for both doses. They concluded that "over the dose range tested buprenorphine displays ceiling in respiratory effect but none in analgesic effect."[71]

The effective analgesic action of BPN is achieved with a relatively low occupancy of receptors (5%–10%). As a result, the analgesia degree is not closely correlated with plasma concentrations.[72] Therapeutic concentrations between 100 and 500 pg/mL are enough to relieve moderate to severe pain.

Pharmaceutical forms and administration

BPN is marketed in the form of SL tablets, tablets, an injectable solution, a transdermal patch, and an oral film.

The administration routes described for the pediatric population are IV; IM; SL; subcutaneous; and neuraxial (peridural/caudal). Other routes of administration are intra-articular and intranasal; however, there is no clinical evidence of these uses in children.[38]

In recent years, the use of a transdermal patch has been evaluated, although in children its safety and efficacy have not been well established.[73] Several case reports have proved that the patch is useful in palliative care patients with pain associated with cancer at doses ranging from 7.5 to 52.5 µg/h.[49,74]

Böhme notes that chronic pain patients treated with transdermal BPN could reduce the total consumption of SL tablets per day by almost 70%, and 50% of cases experienced relief of their severe pain. The highlighted advantages of the transdermal patch are the constant supply of active substance, painless administration, and greater comfort for the patient, all of which have a positive impact on the quality of life.[75]

The transdermal system utilizes a matrix technology, and it is available in patches containing 5, 10, 20, 30, and 40 mg of BPN, with release rates of 5, 10, 35, 52.5, and 70 µg/h, respectively.[76] The diversity of presentations allows an

adequate dose to be administered without cutting the patch. This is a promising therapy in the treatment of chronic pain in children. Dosage regimens used to control pain in children are described in Table 2.

Drug interactions

The main drug interactions can be divided into mild and severe (Table 3). BPN interacts with drugs that cause CNS depression, increasing the risk of overdose.[23] The mechanism of interaction is probably due to additive or synergistic pharmacological effects. Preclinical studies also suggest that benzodiazepines may alter the ceiling effect of respiratory depression induced by BPN.[87]

BPN and its major metabolites cause inhibition of CYP2D6 and CYP3A4; however, this effect is not clinically relevant at therapeutic concentrations with other drugs metabolized by CYP450. Drugs that interfere with CYP3A4, such as erythromycin, ketoconazole, and inhibitors of HIV protease (ritonavir, indinavir, saquinavir) may decrease norbuprenorphine production.[76]

Although 96% of BPN is bound to plasma proteins, there is no competition with transport proteins in the plasma, as BPN binds primarily to globulins α/β.[35]

Coadministration of BPN with other drugs that prolong QT interval may result in additive effects and increase the risk of ventricular arrhythmias and sudden death. Patients with congenital long QT syndrome, conduction abnormalities, or electrolyte abnormalities (eg, loss of magnesium or potassium due to diarrhea or vomiting) are more susceptible to such interactions.[83,84]

When starting BPN administration, it is advisable to prescribe the lowest effective doses and a drug administration at the minimum required, especially in patients receiving another CNS depressant. Close monitoring is also recommended.

Adverse drug reactions

Opioids definitely improve the quality of life among patients with pain; however, the use of these drugs has been limited by fears about safety and tolerability. Adverse reactions with opioids occur in up to 80% of cases, mainly affecting the gastrointestinal tract (30%) and, to a lesser extent, the other organs and systems.[97]

The mild or moderate adverse effects most frequently observed are constipation (25%), somnolence (23%), nausea (21%), dry mouth (17%), and symptoms of vomiting,

Table 2 Dosage and administration routes of buprenorphine in the pediatric population

Dosage form	Route	Indications	Recommended dose	Age (years)
Injectable solution (0.3 mg buprenorphine hydrochloride)	IV	Premedication	1.5–3 μg/kg	3–17[77]
		Postoperative analgesia		0.5–6[15]
		Chronic pain in palliative care	1–6 μg/kg	>0.5[18]
		Chronic pain		
	PCA	Chronic pain in palliative care	3 μg/kg	>0.5[18]
		Postoperative analgesia	(max 150 μg) 6 h	
	CI	Maintenance of mechanical ventilation	0.72–2.16 μg/kg/h	27–32 WGA[55]
		Chronic pain in palliative care	0.5 μg/kg/h (max 30 mg/h)	>0.5[18]
	SC	Pain in palliative care	0.5 μg/kg/h (max 30 μg/h)	>0.5[18]
	Epidural	Postoperative analgesia	2.5–4 μg/kg	11.01[78] 0.5–12[79] 11–13[80]
Sublingual tablets (0.2 mg buprenorphine hydrochloride)	SL	Premedication Chronic pain Postoperative analgesia	3 μg/kg	4.8–15[81]
		Chronic pain in palliative care	4–200 μg/kg/8 h	>0.5[18]
TDS (patch containing 5, 10, 20, 30, or 40 mg buprenorphine)	TDS	Chronic pain in palliative care	Start: 17.5 μg/h End: 35 μg/h	3–5[74]
			Start: 8.75 μg/h End: 35 μg/h	2–17[49]
			5–15 μg/h	3–10[82]

Abbreviations: IV, intravenous; PCA, patient-controlled administration; CI, continuous infusion; SC, subcutaneous; SL, sublingual; TDS, transdermal delivery system; WGA, week gestational age; max, single maximal dose at the start of continuous infusion.

Table 3 BPN pharmacological interactions

Drug	Effect	Management
Severe interactions		
Benzondiazepines, muscle relaxants, anesthetics, antipsychotics, alcohol and opioids	Increases the risk of BPN overdose, hypotension, respiratory depression, coma, and death	Coadministration of these drugs should be avoided
	Alters the usual ceiling effect on respiratory depression induced by BPN	Extreme patient vigilance is required if concomitant use with CNS depressants is necessary[85–88]
	Precipitation of withdrawal symptoms and/or decrease in the analgesic effect of BPN after combination with mixed agonist opioids or antagonists	
Pregabalin	Increases the risk of BPN overdose, hypotension, respiratory depression, coma, and death. Alters the usual ceiling effect on respiratory depression induced by BPN	Coadministration with BPN should be avoided[89]
Escitalopram	Increases the risk of a life-threatening irregular heart rhythm	Caution is advised[90]
Moderate interactions		
Albuterol	Increases the risk of an irregular heart rhythm, which can be serious and fatal; however, this is a rare side effect	Avoid concomitant use[91]
Duloxetine	Dizziness, drowsiness, confusion, and difficulty in concentrating	Coadministration should be avoided[92]
Fluoxetine	Dizziness, drowsiness, confusion, and difficulty in concentrating. Norfluoxetine (active metabolite) inhibits BPN dealkylation	During concomitant use, dosage adjustment may be necessary[92,93]
Quetiapine	Increases the risk of an irregular heart rhythm, which can be serious and life threatening, but is rare	Caution and clinical monitoring if concomitant use is required[94,95]
Laxatives (Senna)	Irregular heartbeat, which can be severe and life threatening, but is rare	Caution in coadministration[96]

Abbreviations: BPN, buprenorphine; CNS, central nervous system.

dizziness, and anorexia (together adding up to 13%). Other effects such as fatigue, diarrhea, insomnia, respiratory depression, and hallucinations add up to ≤5%.[98]

Transdermal administration causes less adverse reactions than other dosage forms, and there are reports of local erythema (25.4%), local pruritus (22%), nausea (11%–16.7%), vomiting (3.7%–9.3%), dizziness (6.8%), fatigue (5.6%), constipation (5.3%–7.8%), sweating (3.7%), somnolence (4%), and headache (1.3%). Swelling and infection at the site of application have been recorded in isolated cases.[19,51,75,99,100] Most side effects at the patch application site are mild or moderate and generally transient.[76]

Epidural BPN administration considerably increased nausea and vomiting events (80%) and slightly increased urinary retention (10%) during the postoperative period.[80] Symptoms of mild hypotension were also observed in 1%–5% of patients.[22]

Data regarding respiratory depression in children are rare. Side effects reported in studies comparing BPN and morphine show that nausea/vomiting occurs in 28% of patients taking BPN versus 16% taking morphine; and urinary retention occurs in 21% of patients taking BPN versus 19% taking morphine. This study did not report the effects on ventilation and BPN was considered safer than morphine in this population.[101]

Respiratory depression induced by BPN can be reversed by administering continuous naloxone infusion (4 mg/h for 30 minutes), with minimal possibility of renarcotization.[102]

Other reports suggest that 0.04–0.10 mg/kg doses of naloxone (maximum 5 mg) successfully reverse the respiratory depression induced by BPN.[19,103–106]

After the abrupt discontinuation of BPN therapy, patients may experience withdrawal symptoms, which are milder than the symptoms associated with other opioids. The possibility of tolerance after short-term treatment is minimal.[19,51]

No hepatic adverse effects have been reported in individuals receiving BPN at analgesic doses.[23] In patients with prolonged therapy (1–2 months), effects such as decreases in erythrocytes number, hemoglobin, hematocrit, and total protein concentration have been observed, which reversed after stopping treatment.[107]

Discussion

The analgesic efficacy of potent opioids such as morphine is well established, and indirect evidence supports opioid use in children and their inclusion in the WHO Model List of Essential Medicines.[16]

Opioids are the basis for the treatment of moderate to severe pain in pediatrics. Although BPN is not the first line of treatment for various pain models, it has been proven to be an effective and safe treatment option for adults.

Due to the vulnerability of the pediatric population and the costs and challenges of conducting clinical studies in children, the current dosage regimen results cannot ensure optimum efficiency and minimal toxicity in these patients.[108]

Data provided by the American Association of Poison Control Centers show that cases of accidental ingestion of BPN in children under 6 years have increased from only two in 2002 to 907 cases in 2008.[109,110] This finding reveals a public health problem and reflects the risk of exposure at home when a family member is using this drug.

A retrospective analysis (3 years) of overdoses in children under 6 years (54 cases) showed that the observed effects included drowsiness/lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation/irritability (5%), and colonic symptoms (2%). No deaths were reported. All children required hospitalization, treatment with opioid antagonists, and/or mechanical ventilation. The study concluded that ingestion of <4 mg of BPN did not cause severe effects and overdoses are generally well tolerated in children.[111]

Compared to adults, BPN in children has a longer clearance related to body weight and a longer duration of action. The risk of inducing respiratory depression when using BPN in combination with other centrally active drugs or opiates is still unknown.[33]

As mentioned earlier, BPN is a drug of clinical interest in pediatrics and it is a choice to consider because of its various formulations and routes of application. BPN also has a prolonged duration of action and metabolism independent of renal function,[33] which is advantageous in controlling postoperative pain[61,80] and neuropathic pain. Furthermore, at analgesic doses, BPN has no effect on the immune system,[19,112] which can be important for cancer pain treatment.

Conclusion

This meta-analysis makes it clear that there are few studies demonstrating the efficacy and safety of BPN use in children. In recent years, this drug has become widespread in the pediatric population; thus, performing controlled clinical trials in this population for adequate pain control is recommended.

Likewise, conducting pharmacological and biosafety studies to develop evidence-based dosing regimens and thereby minimize the risk of adverse effects is a priority.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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