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Oxycodone/Ibuprofen Combination Tablet

A Review of its Use in the Management of Acute Pain

Vicki Oldfield and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

R. Barkin, Department of Anesthesiology, Rush Presbyterian St Luke's Medical Center, Chicago, Illinois, USA; ***R. Dionne***, Clinical Pharmacology Unit, Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, Bethesda, Maryland, USA; ***F. Jamali***, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada; ***G. Pasternak***, Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York, USA; ***R. Pöyhiä***, Department of Anesthesia, Helsinki University Central Hospital, Helsinki, Finland; ***A.B. Shang***, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA; ***N. Singla***, Department of Anesthesia, Huntington Memorial Hospital, Pasadena, California, USA; ***M.T. Smith***, School of Pharmacy, University of Queensland, Brisbane, Queensland, Australia; ***T. Van Dyke***, Clinical Research Centre, Boston University Goldman School of Dental Medicine, Boston, Massachusetts, USA.

Data Selection

Sources: Medical literature published in any language since 1980 on 'oxycodone ibuprofen', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'oxycodone ibuprofen'. Searches were last updated 14 October 2005.

Selection: Studies in patients with acute pain who received oxycodone/ibuprofen. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Ibuprofen, oxycodone, acute pain, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Oxycodone/ibuprofen 5mg/400mg (Combunox™) is an oral fixed-dose combination tablet with analgesic, anti-inflammatory and antipyretic properties. It is approved in the US for the short-term (up to 7 days) management of acute, moderate-to-severe pain and is the first and only fixed-dose combination containing ibuprofen and oxycodone.

A single dose of oxycodone/ibuprofen 5mg/400mg provided better analgesia than low-dose oxycodone or ibuprofen administered alone in most trials and appears to be more effective than a single dose of some other fixed-dose combination analgesics. It is generally well tolerated after single or multiple doses and short-term use is not expected to produce any of the serious adverse effects typically associated with the long-term use of opioids or NSAIDs. Thus, oxycodone/ibuprofen 5mg/400mg is an effective, convenient treatment option for the short-term management of acute, moderate-to-severe pain.

Pharmacological Properties

Oxycodone is a semisynthetic opioid analgesic that appears to act as an agonist at μ- and κ-opioid receptors in the CNS and has additional effects on smooth muscle. Ibuprofen has analgesic, anti-inflammatory and antipyretic properties similar to those of other NSAIDs, and is thought to inhibit the peripheral cyclo-oxygenase (COX) enzymes, COX-1 and COX-2, involved in prostaglandin synthesis. It is usually administered as a racemate, and it appears that (*S*)-ibuprofen accounts for the therapeutic activity of ibuprofen. Coadministration of ibuprofen and oxycodone in mice produces synergistic analgesia; however, clinical trials suggest an additive effect.

An oral dose of oxycodone 5mg is rapidly absorbed, reaching a maximum plasma concentration (C_{max}) in 1–1.5 hours. The extent of oxycodone absorption is dose proportional. Oxycodone undergoes extensive hepatic metabolism to form the primary metabolites noroxycodone, the major circulating metabolite which also possesses weak antinociceptive activity, and oxymorphone, the formation of which is catalysed by cytochrome P450 (CYP) 2D6. Plasma clearance of oxycodone is reduced and plasma half-life is prolonged in patients with renal or hepatic insufficiency.

After administration of a single oral dose of ibuprofen 400mg, C_{max} (24.6 μg/mL) is within the concentration range (11–30 μg/mL) that provided analgesia in 50% of patients in a dental pain model. Both (*R*)- and (*S*)-ibuprofen are extensively (>99%) bound to proteins in plasma. Ibuprofen is metabolised in the liver via oxidation (the primary metabolic route), inversion of (*R*)- to (*S*)-ibuprofen, or glucuronidation. The metabolism and elimination of ibuprofen are impaired in patients with hepatic or renal insufficiency.

The pharmacokinetic properties of oxycodone and ibuprofen are not appreciably altered when they are administered as a fixed-dose combination of oxycodone/ibuprofen 5mg/400mg. Compared with values observed after a single dose, the plasma concentration of oxycodone is increased after multiple 6-hourly doses of oxycodone/ibuprofen 5mg/400mg. Absorption of oxycodone from oxycodone/ibuprofen 5mg/400mg is increased by ≈25% in the presence of food.

Therapeutic Efficacy

In randomised, double-blind, multicentre trials in patients aged ≥12 years with acute, moderate-to-severe pain after dental, abdominal or pelvic surgery, a single oral dose of oxycodone/ibuprofen 5mg/400mg provided significantly more effective analgesia than placebo. Oxycodone/ibuprofen recipients achieved higher mean scores than placebo recipients for total pain relief over 6 hours following administration of the study medication (TOTPAR6) and the sum of pain intensity differences from baseline (SPID6). Patients receiving oxycodone/ibuprofen were less likely to require rescue medication than placebo recipients and had a significantly longer time to remedication. Onset of pain relief was experienced by 90% of oxycodone/ibuprofen recipients compared with 36% of placebo recipients over the 6-hour postadministration period.

In the same well designed trials in patients with dental, abdominal or pelvic pain, oxycodone/ibuprofen provided more effective relief from acute, moderate-to-severe postoperative pain than oxycodone 5mg, oxycodone 10mg, oxycodone/paracetamol (acetaminophen) 5mg/325mg, or hydrocodone/paracetamol 7.5mg/500mg in all studies and than ibuprofen 400mg in two of these studies. Oxycodone/ibuprofen recipients consistently reported significantly better TOTPAR6, SPID6 and global evaluation scores than recipients of comparator preparations, and significantly more oxycodone/ibuprofen recipients reported pain half gone at one hour or over the 6 hours after administration. The time to onset of pain relief (21 or 30 minutes) was significantly faster, and the duration of pain relief was significantly longer, with oxycodone/ibuprofen 5mg/400mg than with ibuprofen 400mg, oxycodone 5mg and hydrocodone/paracetamol 7.5mg/500mg.

Tolerability

Oxycodone/ibuprofen 5mg/400mg was generally well tolerated in patients aged ≥12 years with acute, moderate-to-severe postoperative pain. Nausea, dizziness and somnolence were the treatment-related adverse events that occurred most frequently after a single dose or multiple doses of oxycodone/ibuprofen. Most (52%) adverse events that occurred with multiple doses of oxycodone/ibuprofen were of mild severity.

Fewer patients receiving oxycodone/ibuprofen than those receiving oxycodone/paracetamol 5mg/325mg experienced nausea (6.5% vs 23%) or vomiting (3.2% vs 18%). The rate of withdrawal from treatment because of adverse events was low in patients receiving oxycodone/ibuprofen, and similar to that observed with placebo, oxycodone 5mg or ibuprofen 400mg. Patients who discontinued treatment with oxycodone/ibuprofen generally cited nausea and/or vomiting as the reasons for discontinuation.

1. Introduction

Acute pain is a predictable yet prevalent consequence of surgery or injury. In 2000 and 2001, there were almost 40 million injury-related visits to US hospital emergency departments[1] and, in 2002, 42.5 million inpatient surgical procedures were performed in the US.[2] Acute pain is experienced by up to 80% of patients after surgery, and pain is moderate to severe in up to 86% of these patients.[3,4] Effective treatment of postoperative pain improves the patient's quality of life and is associated with fewer complications, decreased recovery time, shorter hospital stays and reduced health care costs.[3,5] However, postoperative pain may often be inadequately managed;[3,6] according to a recent survey,[6] only 60–76% of postsurgical pain was relieved by analgesic medications.

Acute pain is frequently treated with an oral analgesic, since this is a convenient and cost-effective route of administration.[5] Mild-to-moderate pain is generally treated with non-opioid analgesics, such as aspirin, paracetamol (acetaminophen) or an NSAID,[5] whereas opioid analgesics are generally the mainstay of treatment of moderate-to-severe pain.[5,7]

Multimodal analgesia, which involves the concurrent use of analgesics with different mechanisms of action, is frequently recommended for the relief of acute, moderate-to-severe pain.[8-10] By simultaneously addressing different mechanisms involved in pain sensation, better analgesia is produced than that achieved with an individual analgesic.[11] Non-opioid and opioid analgesics can be combined to simultaneously address both peripheral and central mechanisms involved in pain sensation.[11] Various studies have demonstrated synergistic pain relief with the use of such combinations (as reviewed by Barkin[8]). The enhanced analgesia achieved by use of a combination of analgesics may allow for a reduction in the dose of the components and better tolerability.[8,11] When an NSAID is combined with an opioid, the opioid requirement is decreased by up to 30%, thus reducing the incidence of opioid-related sedative and emetic adverse effects.[11]

Fixed-dose, combination analgesic preparations are a simple and convenient means of administering analgesics for the relief of acute pain.[5] Oxycodone/ibuprofen 5mg/400mg (Combunox™)[1], which is currently available in the US only, is a fixed-dose combination analgesic approved for the short-term treatment of acute, moderate-to-severe pain.[12] It is the first and only fixed-dose combination containing the NSAID ibuprofen, a short-acting NSAID preferred for use in patients with acute pain, and oxycodone, an opioid analgesic. This review focuses on the use of the fixed-dose combination of oxycodone/ibuprofen 5mg/400mg in the management of acute, moderate-to-severe pain.

2. Pharmacodynamic Properties

The pharmacodynamic activities of oxycodone and ibuprofen are reviewed elsewhere[13,14] and are, therefore, discussed only briefly in this section. Data on the pharmacodynamic effects of oxycodone and ibuprofen when administered in combination are currently limited.

2.1 Oxycodone

Oxycodone is a semisynthetic opioid analgesic.[14,19] The mechanism by which oxycodone produces an antinociceptive effect is unknown, but it appears to act as an agonist at μ- and κ-opioid receptors in the CNS and has additional effects on smooth muscle (table I).[14,20] Like other opioid ago-

Table I. Overview of the pharmacodynamic profile of oxycodone

Mechanism of action
μ- and κ-opioid receptor agonist[14]
Effects on the CNS
Dose-dependent antinociception and CNS depression in rats [15]
Dose-dependent antinociception, decreased respiratory rate and volume, increased muscle tone, increased spontaneous motor activity, reduced spontaneous gastric motility and potentiation of anaesthesia in mice and rats[16]
Respiratory depression in healthy volunteers[17] and patients undergoing minor surgery[18]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

nists, oxycodone causes respiratory depression,[17,18] nausea[21] and increased serum prolactin levels in humans.[21] Oxycodone is expected to cause additive CNS depression when administered in conjunction with other CNS depressants[12] and, as with other opioid analgesics, long-term use of oxycodone may produce tolerance and physical dependence.[22] The addictive potential of oxycodone is similar to that of morphine.[21] Unlike morphine, oxycodone does not cause a rise in mean arterial pressure and heart rate.[17,18]

2.2 Ibuprofen

Ibuprofen is a propionic acid derivative that, like other NSAIDs, has analgesic, anti-inflammatory and antipyretic properties.[13,19] Although the exact mechanism of action of ibuprofen is not completely understood, its effects are believed to be mediated via inhibition of the peripheral cyclo-oxygenase (COX) enzymes, COX-1 and COX-2, which are involved in prostaglandin synthesis (table II).[13,19] Oral ibuprofen 800mg administered three times daily to healthy human volunteers inhibited 88.7% of COX-1 activity and 71.4% of COX-2 activity.[23] Ibuprofen may have additional peripheral anti-inflammatory activity independent of its action at COX-1 and COX-2 enzymes, such as inhibition of neutrophil activity and action at leukocytes to prevent inflammatory oedema.[13] Central mechanisms for analgesia may include COX-2 inhibition, prevention of the spinal release of excitatory amino acids involved in nociception and downregulation of nitric oxide production (table II).[13,24]

Ibuprofen is usually administered as a racemate, and the (*R*)-[−]-enantiomer [(*R*)-ibuprofen] is converted to the (*S*)-[+]-enantiomer [(*S*)-ibuprofen] in plasma after absorption (section 3.2).[12,13] (*S*)-ibuprofen appears to account for the therapeutic activity of ibuprofen; it was >100-fold more effective than (*R*)-ibuprofen at inhibiting prostaglandin synthesis in *in vitro* animal studies.[13] A serum concentration of 11–30 μg/mL of racemic ibuprofen was required for complete pain relief in 50% of patients after third-molar extraction.[25] However, the analgesic effect of ibuprofen may be delayed or compromised in patients with post-surgical dental pain, since the absorption of ibuprofen has been found to be reduced in these patients (section 3.2).[26]

Table II. Overview of the pharmacodynamic profile of ibuprofen

Mechanism of action
Inhibition of peripheral COX-1 and COX-2 enzymes[13,23]
Central effects
COX-2 enzyme inhibition[13]
Inhibition of spinal release of excitatory amino acids and substance P[13]
Downregulation of nitric oxide production[24]
Peripheral effects
Action at polymorphonuclear leukocytes and neutrophils[13]

COX = cyclo-oxygenase.

2.3 Oxycodone plus Ibuprofen

Synergistic analgesia when ibuprofen is administered in conjunction with oxycodone has been demonstrated in animal studies,[27,28] consistent with evidence of synergy between ibuprofen and other opioids, such as codeine and hydrocodone, in animal studies.[29,30] In the phenyl-p-benzoquinone writhing test model of pain in mice, various fixed-ratio doses of oxycodone : ibuprofen (1 : 1.25, 1 : 3.12, 1 : 6.24, 1 : 12.5 and 1 : 31.1) provided analgesia in significantly more mice than either oxycodone or ibuprofen administered alone ($p < 0.016$).[28] In the radiant heat tail-flick model of moderate-to-severe pain in mice, a significantly lower dose of oxycodone was required to produce 50% analgesia when ibuprofen and oxycodone were administered together than when oxycodone was administered alone (0.53 vs 1.9 mg/kg; $p < 0.05$).[27]

3. Pharmacokinetic Properties

The individual pharmacokinetic parameters of oxycodone and ibuprofen, which have been reviewed previously,[13,31] are discussed in section 3.1 and section 3.2, while section 3.3 focuses on the pharmacokinetic properties of oxycodone and ibuprofen administered in combination. Tables III and IV summarise the pharmacokinetic parameters of oxycodone and ibuprofen administered alone and in combination.[32,33]

Table III. Pharmacokinetic properties of oral oxycodone following administration alone or as a fixed-dose combination with ibuprofen. Healthy volunteers[32] and patients (pts) with acute, moderate-to-severe postoperative dental pain[33] received single doses of oral oxycodone 5mg (OXY) or oxycodone/ibuprofen 5mg/400mg (OXY/IBU). Mean values are reported

Parameter	Healthy volunteers[32]		Pts with acute, moderate-to-severe postoperative dental pain[33]	
	OXY (n = 23)	OXY/IBU (n = 23)	OXY (n = 3)	OXY/IBU (n = 12)
C_{max} (ng/mL)	7.6	7.5	13.6	11.6
t_{max} (h)	1.4	1.3	1.1	2.1
AUC (ng • h/mL)	36.0[a,b]	36.5[a,b]	35.9[c]	35.8[c]
$t_{½}$ (h)	2.6[b]	2.7[b]	3.2	2.9

a From time 0 to infinity.

b n = 17; analysis excludes 6 volunteers who did not have a terminal elimination phase to allow calculation of AUC_{∞}.

c From time 0 to time of the last measurable concentration.

AUC = area under the plasma concentration-time curve; $\mathbf{C}_{max}$ = maximum plasma concentration; $\mathbf{t}_{½}$ = elimination half-life; $\mathbf{t}_{max}$ = time to reach C_{max}.

3.1 Oxycodone

An oral dose of oxycodone 5mg is rapidly absorbed in healthy volunteers and in patients with acute, moderate-to-severe pain, reaching maximum plasma concentrations (C_{max}) in 1.4 and 1.1 hours (table III).[32,33] The extent of absorption is dose proportional; in a study of oxycodone in healthy volunteers (available as an abstract),[34] C_{max} and the mean area under the plasma concentration-time curve (AUC) after administration of a single dose of oral oxycodone 5mg were 9.7 ng/mL and 50.7 ng • h/mL, respectively, compared with 42.9 ng/mL and 296.8 ng • h/mL after administration of oxycodone 30mg. Oxycodone is ≈45% bound to serum proteins[35] and has high oral bioavailability (60–87%[36,37]) compared with morphine.[37] After a high-fat meal, oxycodone C_{max} is reduced by ≈20% and the AUC is increased by ≈20%, suggesting a slower rate of absorption but improved bioavailability.[31]

Oxycodone undergoes extensive hepatic metabolism via *N*- and *O*-demethylation, 6-ketoreduction and glucuronidation;[31] <1% of an oral dose of oxycodone is excreted unchanged in the urine.[38] The primary metabolites are noroxycodone,[39] the major circulating metabolite which also possesses weak analgesic activity,[31] and oxymorphone, the formation of which is catalysed by cytochrome P450 (CYP) 2D6,[40] conferring the potential for interactions with drugs which block the CYP2D6 metabolic pathway (section 4).[31] The elimination half-life ($t_{½}$) of oxycodone (2.6 or 3.2 hours after oral administration; table III) is independent of dose.[37,41] Renal clearance was 0.084 L/min after oral administration of oxycodone 0.28 mg/kg in healthy volunteers.[41]

In patients with renal insufficiency or hepatic impairment, oxycodone plasma clearance is reduced and $t_{½}$ is prolonged, resulting in greater exposure (AUC) to oxycodone.[42,43] The pharmacokinetic properties of oxycodone in the elderly (aged >65 years) are generally similar to those observed in younger adults.[31]

3.2 Ibuprofen

The pharmacokinetic properties of ibuprofen have been reviewed elsewhere[13] and, therefore, are discussed only briefly in this section.

After administration of a single oral 400mg dose of ibuprofen, C_{max} (32 and 25 μg/mL in healthy volunteers and in patients with pain; table IV) was

Table IV. Pharmacokinetic properties of oral ibuprofen following administration alone or as a fixed-dose combination with oxycodone. Healthy volunteers[32] and patients (pts) with acute, moderate-to-severe postoperative dental pain[33] received single doses of oral ibuprofen 400mg (IBU) or oxycodone/ibuprofen 5mg/400mg (OXY/IBU). Mean values are reported

Parameter	Healthy volunteers[32]		Pts with acute, moderate-to-severe postoperative dental pain[33]	
	IBU (n = 22)[a]	OXY/IBU (n = 23)	IBU (n = 12)	OXY/IBU (n = 12)
C_{max} (μg/mL)	32.2	32.1	24.6	18.5
t_{max} (h)	1.3	1.5	2.4	3.1
AUC[b] (μg • mL/h)	116.0	116.5	72.7	58.7
$t_{½}$ (h)	1.9	1.9	1.9	2.6

a n = 22; analysis excludes one volunteer with very low ibuprofen concentrations.

b From time 0 to time of the last measureable concentration.

AUC = area under the plasma concentration-time curve; $\mathbf{C}_{max}$ = maximum plasma concentration; $\mathbf{t}_{½}$ = elimination half-life; $\mathbf{t}_{max}$ = time to reach C_{max}.

similar to the range of concentrations that provided complete analgesia in 50% of patients in the dental pain model described in section 2.2 (11–30 μg/mL).[25,32,33] Both (*R*)- and (*S*)-ibuprofen are extensively (>99%) bound to proteins in plasma.[12,13] The C_{max} and AUC of ibuprofen after a 600mg dose were significantly reduced after dental surgery, compared with values observed before surgery ($p < 0.05$), possibly because of a stress-related reduction in gastric absorption of ibuprofen.[26]

Ibuprofen is extensively metabolised in the liver via oxidation (the primary metabolic route), inversion of (*R*)- to (*S*)-ibuprofen, or glucuronidation; <0.2% of an ibuprofen dose is excreted unchanged.[12,13] The main metabolites are (+)-2,4′-(2-hydroxy-2-methylpropyl) phenylpropionic acid and (+)-2,4′-(2-carboxypropyl) phenylpropionic acid.[12] After oral administration of racemic ibuprofen, >60% of (*R*)-ibuprofen is converted to (*S*)-ibuprofen, the pharmacologically active enantiomer (section 2.2), in the liver.[13]

The metabolism and elimination of ibuprofen are impaired in patients with hepatic or renal insufficiency.[13] The $t_{1/2}$ of ibuprofen is increased in patients with impaired hepatic function[13] and, like other NSAIDs, ibuprofen may cause elevation of liver enzyme levels.[12] Inhibition of prostaglandin synthesis by ibuprofen (section 2.2) may exacerbate renal dysfunction in patients with conditions such as renal insufficiency, heart failure and liver impairment, where renal prostaglandins act in a compensatory manner to dilate the renal artery and enhance renal perfusion,[13] and may affect the actions of concomitantly administered drugs (section 4).[12]

3.3 Oxycodone/Ibuprofen

The pharmacokinetic properties of oxycodone/ibuprofen administered as a fixed-dose combination have been investigated in two studies in healthy volunteers[32] and in patients with acute, moderate-to-severe postoperative dental pain.[33] Information from the manufacturer's prescribing information is also discussed.[12]

The pharmacokinetic properties of single-dose oxycodone and ibuprofen after administration of the fixed-dose combination are broadly similar to those observed after administration of each agent individually, except that the C_{max} values for oxycodone and ibuprofen were reached 1 and 0.7 hours later in patients with dental pain receiving the combination (tables III and IV).[32,33]

The plasma concentration of oxycodone is increased after multiple doses of oxycodone/ibuprofen 5mg/400mg compared with values observed after a single dose of oxycodone/ibuprofen 5mg/400mg;[12] after repeated (6-hourly) administration of oxycodone/ibuprofen 5mg/400mg, oxycodone C_{max} increased by 50–65%.[12] The extent of absorption of oxycodone from the combination formulation is increased in the presence of food by ≈25%.[32] The plasma concentration and bioavailability of ibuprofen are unchanged after multiple-dose administration of oxycodone/ibuprofen 5mg/400mg and in the presence of food.[12]

No data are available on the pharmacokinetic properties of oxycodone/ibuprofen 5mg/400mg when administered to patients with renal or hepatic impairment.[12] However, contraindications, warnings and precautions apply to the use of oxycodone/ibuprofen 5mg/400mg in these populations based on the altered pharmacokinetic properties observed after individual administration of oxycodone and ibuprofen in patients with hepatic or renal impairment (section 7).[12]

4. Drug Interactions

Oxycodone and ibuprofen are associated with a range of potential pharmacodynamic and pharmacokinetic drug interactions which are discussed in the manufacturer's prescribing information[12] and briefly reviewed in this section.

The effects of oxycodone may be enhanced by other CNS depressants (causing additive CNS depression) or monoamine oxidase inhibitors, whereas oxycodone may intensify the action of neuromuscular blocking agents.[12] Concomitant administration of oxycodone and mixed opioid agonist/antagonist drugs may produce reduced analgesia or withdrawal symptoms; the concurrent use of anticholinergics may precipitate paralytic ileus. Oxycodone may

interact with drugs that block the actions of CYP2D6, since this enzyme is involved in the metabolism of oxycodone (section 3.1).[31]

When ibuprofen is administered in conjunction with other NSAIDs or warfarin, an additive effect on gastrointestinal bleeding may result.[12] The inhibition of renal prostaglandin synthesis by ibuprofen may reduce the natriuretic effect of furosemide and thiazide diuretics and may impair the renal clearance of lithium.[12]

5. Therapeutic Efficacy

The analgesic efficacy of a single dose of oral oxycodone/ibuprofen 5mg/400mg was evaluated versus placebo or other analgesics in patients with acute, moderate-to-severe, postoperative pain.[33,44-47] Studies were conducted in patients with pain after dental (section 5.1)[33,44,46,47] or abdominal or pelvic surgery (section 5.2).[45]

5.1 In Patients with Dental Pain

Four randomised, double-blind, placebo- and active-controlled, multicentre trials ($n \geq 118$)[33,44,46,47] used the dental pain model to assess the analgesic efficacy of a single dose of oxycodone/ibuprofen 5mg/400mg in patients with acute, moderate-to-severe pain. This is a well established clinical model for the evaluation of analgesics in oral surgery outpatients who experience moderate-to-severe pain after surgical extraction of impacted third molars.[48] Results from one trial are available as a poster only[46] and additional data from one fully published trial[44] are reported in a poster.[49] Data from a pooled analysis (available as an abstract plus poster)[50] that includes results from two single-dose studies, plus limited data from a supporting multiple-dose study are also discussed briefly. Two single-dose trials[46,47] evaluated a range of doses of oxycodone/ibuprofen; results discussed in this section focus on the approved dose only (oxycodone/ibuprofen 5mg/400mg).

Patients were men and women aged, where specified, ≥16[33] or ≥12[44,46] years; however, the youngest patient enrolled was aged 14 years.[51] Patients reported post-surgical pain as moderate to severe in a diary[33,44] or as 'moderate' when questioned by an investigator[47] and/or recorded a score of ≥50mm on a 100mm visual analogue scale (VAS) of pain intensity within 5 hours of surgery before receiving study medication.[33,44,46] Patients were randomised to receive oxycodone/ibuprofen 5mg/400mg,[33,44,46,47] ibuprofen 400mg,[33,46,47] oxycodone 5mg,[33,46] oxycodone 10mg,[46] oxycodone/paracetamol 5mg/325mg,[44] hydrocodone/paracetamol 7.5mg/500mg,[44] other doses of oxycodone/ibuprofen (not discussed further)[46,47] or placebo.[33,44,46]

Patients were excluded if they had taken analgesic or anti-inflammatory agents, opiate antagonists, steroids or psychoactive drugs up to 72 hours prior to surgery.[33,44,46,47] Patients were required to abstain from alcohol, caffeine and tobacco for 8 hours prior to surgery and during the postadministration observation period, and rescue medication was available if the study medication did not provide adequate analgesia.[33,44]

In three trials,[33,44,46] the primary endpoints were total pain relief (TOTPAR) over 6 hours after administration of the study medication (TOTPAR6) and the sum of pain intensity differences from baseline (SPID) over the 6-hour postadministration period (SPID6) in the intention-to-treat (ITT) population. At 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours after drug administration, patients completed Likert scales to rate pain intensity (none [0], slight [1], moderate [2] or severe [3]) and pain relief (no pain relief [0], a little pain relief [1], some pain relief [2], a lot of relief [3], complete relief [4]). Pain intensity difference was the difference from baseline in the pain intensity score at each time point. TOTPAR6 and SPID6 were calculated based on the area under the pain relief-time and pain intensity difference-time curves from 0 to 6 hours.[33,44,46] Secondary endpoints included TOTPAR3 and SPID3 (calculated over the 3-hour postadministration period),[33,44] peak pain relief, pain relief at each time point, peak pain intensity difference from baseline, pain intensity difference at each time point, time to onset of pain relief, proportion of patients reporting pain half gone, time to remedication and the patient's global evaluation.[33,44] In the other trial,[47] pain relief and

Table V. Analgesic efficacy of a single dose of oral oxycodone/ibuprofen 5mg/400mg (OXY/IBU) in patients (pts) with acute, moderate-to-severe pain.[33,44-46] Pts were adults who underwent surgical extraction of two or more impacted third molars in studies based on the dental model of acute pain[33,44,46] or women who underwent abdominal or pelvic surgery.[45] Efficacy assessments were performed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours after administration of the study medication. Total pain relief (TOTPAR) and the sum of the pain intensity differences from baseline (SPID) were calculated from the area under the pain relief-time and pain intensity difference-time curves from 0 to 6 hours (TOTPAR6, SPID6) [primary endpoints] and 0 to 3 hours (TOTPAR3, SPID3). Mean[44] or least squares mean[33,45,46] values are presented

Study	Treatment (no. of pts)	Results			
		TOTPAR6[a]	TOTPAR3[b]	SPID6[c]	SPID3[d]
Dental pain					
Christensen et al.[46]	OXY/IBU (171)	15.76*†		8.28*†	
	IBU (171)	14.46*		7.39*	
	OXY (57)	8.62*		3.30*	
	OXY 10 (57)	8.91*		3.37*	
	PL (57)	6.27		1.74	
Litkowski et al.[44]	OXY/IBU (62)	14.98**††	6.43**††	7.78**††	3.27**††
	OXY/PAR (61)	9.53**	4.78**	3.58**	1.85**
	HYD/PAR (62)	8.36**	4.29**	3.32*	1.87**
	PL (63)	5.05	2.29	0.69	0.24
Van Dyke et al.[33]	OXY/IBU (186)	13.3**‡‡§	6.43**††	6.54**‡‡§	3.19**††
	IBU (186)	12.2**‡‡	5.35**‡‡	5.41**‡‡	2.43**‡‡
	OXY (63)	4.3	2.17	0.14	0.27
	PL (62)	4.2	2.03	0.32	0.24
Abdominal or pelvic pain					
Singla et al.[45]	OXY/IBU (168)	11.75**‡§		5.81**‡‡§	
	IBU (174)	10.03[e]		4.64[e]	
	OXY (52)	8.56[e]		3.08[e]	
	PL (60)	6.41		2.37	

a Where specified, the range of potential scores was 0 to 24.[33,44]

b The range of potential scores was 0 to 12.[33,44]

c Where specified, the range of potential scores was −6 to 18[44] or −6 to 12.[33]

d The range of potential scores was −3 to 6[33] or −3 to 9.[44]

e Statistical analyses not reported.[45]

HYD/PAR = hydrocodone/paracetamol 7.5mg/500mg; **IBU** = ibuprofen 400mg; **OXY** = oxycodone 5mg; **OXY 10** = oxycodone 10mg; **OXY/PAR** = oxycodone/paracetamol 5mg/325mg; **PL** = placebo; * $p \leq 0.05$, ** $p < 0.001$ vs PL; † $p \leq 0.05$, †† $p < 0.001$ vs each active comparator in the same study; ‡ $p < 0.01$, ‡‡ $p < 0.001$ vs OXY; § $p < 0.05$ vs IBU.

pain intensity were assessed using Likert scales and VAS scores.

At baseline, there were no significant between-group differences in pain intensity scores, and demographics were generally similar across treatment groups.[33,44,46,47] There were significant differences between the oxycodone/ibuprofen and placebo treatment groups at baseline with respect to sex ($p = 0.041$) and race ($p = 0.023$) in one trial.[33] However, analyses of the primary endpoints with adjustments for race and sex found that treatment efficacy was not affected by these characteristics.[33] There were also significant between-group differences at baseline with regard to race ($p = 0.048$) and weight ($p = 0.003$) in another trial;[44] the authors report that these differences were unlikely to have affected treatment efficacy.

5.1.1 Comparisons with Placebo

A single dose of oral oxycodone/ibuprofen was significantly more effective than placebo for relief from acute, moderate-to-severe dental pain.[33,44,46] Compared with placebo recipients, oxycodone/ibuprofen recipients achieved significantly better total pain relief (TOTPAR6) and a greater sum of

Table VI. Analgesic efficacy of a single dose of oral oxycodone/ibuprofen 5mg/400mg (OXY/IBU) in patients (pts) with acute, moderate-to-severe pain.[33,44,45,49] Pts were adults who underwent surgical extraction of two or more impacted third molars in studies based on the dental model of acute pain[33,44] or women who underwent abdominal or pelvic surgery.[45] Efficacy assessments were performed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours after administration of the study medication. Mean[44,49] or least squares mean[33,45] values for some secondary endpoints are depicted

Study	Treatment (no. of pts)	Median time to onset of pain relief (min)[a]	Peak pain relief score[b]	Peak pain intensity difference score[c]	Pts requiring remedication (%)	Median time to remedication (h)	Pts reporting pain half gone (%)[d]	Global evaluation[e]
Dental pain								
Litkowski et al.[44,49]	OXY/IBU (62)	30.4***§	3.40***†††	1.82***††	17.7***†††	NA[g]	89[f]***†††	2.61***†††
	OXY/PAR (61)	28.2***	2.67***	1.34***	49.2**	NA[g]	51[f]**	1.79***
	HYD/PAR (62)	41.1**	2.29***	1.15***	61.3	4.17	52[f]***	1.6***
	PL (63)	NA[g]	1.62	0.73	73.0	2.14	23[f]	0.67
Van Dyke et al.[33]	OXY/IBU (186)	21.4*†	3.13*†	1.61**††	36.4***‡‡	NA[g]	74.9[h]*†	2.63**††
	IBU (186)	29.7***‡‡	2.87***‡‡	1.35***‡‡	37.6***‡‡	NA[g]	59.1[h]***‡‡	2.26***‡‡
	OXY (63)	NA[g]	1.43	0.56	82.5	2.10	19[h]	0.66
	PL (62)	NA[g]	1.34	0.59	83.9	2.03	14.5[h]	0.5
Abdominal or pelvic pain								
Singla et al.[45]	OXY/IBU (168)		2.61**	1.46**‡	55.0[i]	5.23†		2.2***‡‡#
	IBU (174)		2.38	1.38*	70.7	3.95		1.92
	OXY (52)		2.32	1.17	84.6	2.50		1.38
	PL (60)		2.01	1.13		2.28		1.23

a As per pt self-assessment using a stopwatch.

b Pts completed the statement "My relief from starting pain is: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete."

c Pts completed the statement "My pain at this time is: 0 = none; 1 = slight; 2 = moderate; 3 = severe."

d Pts completed the statement "My pain at this time is half gone: 1 = yes; 2 = no."

e At 6 hours postadministration or at the time of remedication or premature termination (whichever occurred first), pts answered the question "How would you rate the study medication you received for pain?: 0 = poor; 1 = fair; 2 = good; 3 = very good; 4 = excellent."

f During the 6-hour postadministration period.

g Could not be calculated because <50% of pts experienced this endpoint.

h At 1 hour postadministration.

i Statistical analysis not reported.

HYD/PAR = hydrocodone/paracetamol 7.5mg/500mg; **IBU** = ibuprofen 400mg; **NA** = not available; **OXY** = oxycodone 5mg; **OXY/PAR** = oxycodone/paracetamol 5mg/325mg; **PL** = placebo; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ vs each active comparator in the same study; ‡ $p < 0.05$, ‡‡ $p < 0.001$ vs OXY; § $p < 0.002$ vs HYD/PAR; # $p < 0.05$ vs IBU.

pain intensity difference from baseline (SPID6) score (table V).[33,44,46]

Patients receiving oxycodone/ibuprofen also reported higher scores for TOTPAR3 and SPID3 (table V) and peak pain relief and peak pain intensity difference from baseline than placebo recipients (table VI).[33,44] Significantly more oxycodone/ibuprofen than placebo recipients experienced the onset of pain relief during the 6-hour postadministration period (90% vs 36%; $p < 0.001$).[33] Pain relief appeared to last longer with oxycodone/ibuprofen than with placebo; the time to remedication could not be determined for oxycodone/ibuprofen recipients in two trials because <50% of patients in these treatment groups required rescue medication.[33,44] In comparison, 73%[44] and 84%[33] of placebo recipients in these trials required rescue medication ≈2 hours after administration of the study drug.

Significantly fewer oxycodone/ibuprofen than placebo recipients withdrew from the trials (37% vs 84%; $p < 0.001$[33] and 18% vs 73%; statistical analysis not reported),[44] and the majority of patients who withdrew from the trials cited an insuffi-

cient therapeutic response as the primary reason for discontinuation.[33,44]

5.1.2 Comparisons with Other Analgesics

Oxycodone/ibuprofen provided better relief from acute, moderate-to-severe dental pain than either component individually according to the primary endpoints in three (table V)[33,44,46] of four trials; one trial found no difference in peak pain relief or pain intensity difference scores between oxycodone/ibuprofen and ibuprofen 400mg.[47] Primary endpoints also indicated that patients achieved superior pain relief with oxycodone/ibuprofen than with oxycodone/paracetamol 5mg/325mg, and hydrocodone/paracetamol 7.5mg/500mg (table V).[44]

Patients receiving oxycodone/ibuprofen also experienced significantly better TOTPAR3 and SPID3 than patients receiving other treatments (table V) and had significantly higher global evaluation scores (table VI).[33,44] Significantly more oxycodone/ibuprofen recipients reported pain half gone at 1 hour after administration[33] and over the 6-hour postadministration period.[44]

Oxycodone/ibuprofen provided rapid onset of pain relief (median time 21[33] and 30[44] minutes; table VI). The onset of pain relief was significantly faster with oxycodone/ibuprofen than with ibuprofen 400mg,[33] oxycodone 5mg,[33] and hydrocodone/paracetamol 7.5mg/500mg[44] (table VI) and was similar to that observed with oxycodone/paracetamol 5mg/325mg (28 min).[44] Analgesia (self-assessed by patients using a stopwatch) occurred ≈30% more quickly with oxycodone/ibuprofen than with ibuprofen 400mg alone (21 vs 30 minutes; $p < 0.001$).[33] An analysis of pooled data[50] suggests that the greatest differences in mean pain relief and mean pain intensity difference scores between the oxycodone/ibuprofen, ibuprofen 400mg and oxycodone 5mg treatment groups occurred during the first 2 hours after drug administration; after 2 hours postadministration mean pain relief and pain intensity difference scores were similar for the oxycodone/ibuprofen and ibuprofen 400mg treatment groups.[50]

Rescue medication was required by significantly fewer oxycodone/ibuprofen recipients than patients who received ibuprofen 400mg,[33] oxycodone 5mg,[33] oxycodone/paracetamol 5mg/325mg[49] or hydrocodone/paracetamol 7.5mg/500mg (table VI).[49] The time to remedication could not be determined for oxycodone/ibuprofen recipients because <50% of patients experienced this endpoint (table VI).[33,44]

Fewer oxycodone/ibuprofen recipients (18–37%) discontinued treatment compared with those who received oxycodone 5mg (83%),[33] oxycodone/paracetamol 5mg/325mg (64%)[44] and hydrocodone/paracetamol 7.5mg/500mg (73%)[44] [$p < 0.001$ vs oxycodone 5mg;[33] statistical analyses not reported for the other comparisons[44]]. The majority of patients who discontinued treatment cited the primary reason as insufficient therapeutic response.[33,44]

Patients in the multiple dose study received oxycodone/ibuprofen 5mg/400mg every 6 hours for up to 7 days and were asked to provide a global evaluation of efficacy; over 75% of oxycodone/ibuprofen recipients rated the combination as 'excellent' or 'very good'.[50]

5.2 In Patients with Abdominal or Pelvic Pain

One large (n = 456), randomised, double-blind, multicentre trial in patients with acute, moderate-to-severe pain following abdominal or pelvic surgery compared the analgesic efficacy of a single dose of oral oxycodone/ibuprofen 5mg/400mg with placebo or ibuprofen administered alone.[45]

Patients were women aged ≥18 years who received post-surgery patient-controlled analgesia (PCA) which was discontinued on the morning of the day after surgery.[45] Women who requested analgesia within 6 hours after discontinuation of PCA, had moderate-to-severe pain on a 4-point Likert scale of pain intensity, and had a VAS pain intensity score ≥50mm were randomised to receive oxycodone/ibuprofen 5mg/400mg, ibuprofen 400mg, oxycodone 5mg or placebo.[45] Patients were excluded if they had taken analgesic or anti-inflammatory agents, opiate antagonists, steroids or psychoactive drugs up to 72 hours prior to surgery and were required to abstain from alcohol, caffeine

and tobacco for 8 hours prior to surgery and during the 6-hour postadministration observation period. Rescue medication was available if the study medication did not provide adequate analgesia.[45]

TOTPAR6 and SPID6 in the ITT population were the primary endpoints.[45] Secondary endpoints included pain relief and pain intensity difference at each time point, peak pain relief and peak pain intensity difference, time to use of rescue medication, time to onset of pain relief, proportion of patients reporting pain half gone, and the patient's global evaluation.[45] There were no significant between-group differences in pain intensity scores at baseline and demographics were generally similar across treatment groups.[45]

5.2.1 Comparisons with Placebo

Patients with acute, moderate-to-severe pain after abdominal or pelvic surgery experienced significantly better pain relief with oxycodone/ibuprofen than with placebo.[45] Compared with placebo recipients, patients who received oxycodone/ibuprofen had significantly better TOTPAR6 and SPID6 scores (table V) and peak pain relief and peak pain intensity difference scores (table VI).[45] Pain relief lasted for longer with oxycodone/ibuprofen than with placebo; the estimated time to the use of rescue medication was 5.23 hours with oxycodone/ibuprofen versus 2.28 hours with placebo ($p < 0.05$).[45]

5.2.2 Comparisons with Other Analgesics

Oxycodone/ibuprofen provided significantly better relief from acute, moderate-to-severe pain after abdominal or pelvic surgery than ibuprofen 400mg or oxycodone 5mg alone, according to TOTPAR6 and SPID6 scores (table V).[45]

Compared with patients who received oxycodone 5mg or ibuprofen 400mg alone, oxycodone/ibuprofen recipients had significantly better global evaluation scores, and experienced analgesia for a significantly longer time (table VI).[45] The onset of pain relief was experienced by 68.5% of oxycodone/ibuprofen recipients compared with 57.7% and 62.1% of oxycodone 5mg and ibuprofen 400mg recipients, respectively (statistical analysis not reported). There were no significant differences between oxycodone/ibuprofen and either agent alone with respect to peak pain relief or between oxycodone/ibuprofen and ibuprofen alone in peak pain intensity difference scores; the peak pain intensity difference score with oxycodone/ibuprofen was significantly higher than that observed with oxycodone 5mg (table VI). Fewer oxycodone/ibuprofen than ibuprofen 400mg or oxycodone 5mg recipients required rescue medication (table VI; statistical analysis not reported).[45]

6. Tolerability

The tolerability profiles of oxycodone and ibuprofen administered as single agents are well understood.[14,52] Adverse events observed with oxycodone are similar to those observed with other opioid agonists and include dose-dependent respiratory depression, hypotension, nausea, constipation, vomiting and headache.[14,22] Like other NSAIDs, ibuprofen may cause serious gastrointestinal adverse effects such as inflammation, bleeding and ulceration,[52] but at therapeutic doses the risk of serious upper gastrointestinal toxicity with ibuprofen is relatively low compared with other NSAIDs.[53] This section focuses on the tolerability of oxycodone and ibuprofen administered as the fixed-dose combination.

Tolerability data for oxycodone/ibuprofen 5mg/400mg are available from trials discussed in section 5.[33,44-47] Additional information is presented from a pooled analysis of tolerability data from seven single-dose studies (n = 2651) and one multiple-dose study, in which 247 patients who completed a single-dose study were randomised to receive oxycodone/ibuprofen 5mg/400mg up to four times per day at 6-hour intervals, to a maximum of 27 doses (available as an abstract plus poster).[54] The multiple-dose study also included an oxycodone/ibuprofen 10mg/400mg treatment arm (n = 241);[54] results from patients who received this dose are not discussed in this section. The manufacturer's prescribing information also includes a pooled analysis of results from single-dose trials (n = 2437) and a multiple-dose trial (n = 334).[12]

Oxycodone/ibuprofen was generally well tolerated in patients aged ≥12 years with acute, moderate-

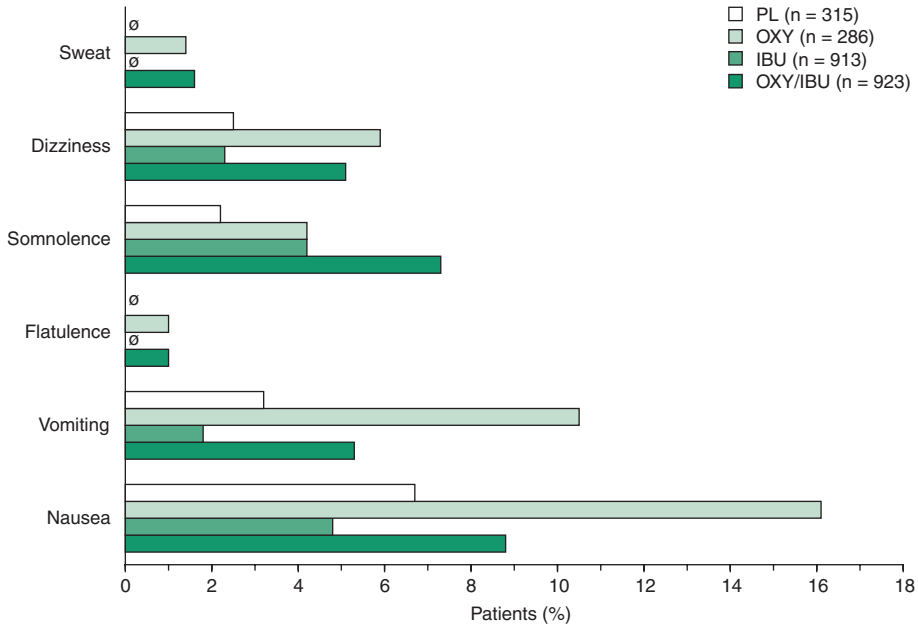

Fig. 1. Tolerability of a single dose of oral oxycodone/ibuprofen 5mg/400mg (OXY/IBU) in patients with acute, moderate-to-severe pain. Data are from a pooled analysis of clinical trials (n = 2437) in which patients with postoperative dental, abdominal or pelvic pain received a single dose of OXY/IBU, ibuprofen 400mg (IBU), oxycodone 5mg (OXY) or placebo (PL). Adverse events depicted are those that occurred in ≥1% of patients and at a higher incidence than that in the PL treatment groups (statistical analyses not reported).[12] **ø** indicates incidence of <1%.

to-severe postoperative pain.[12,33,44-47] Adverse events of any kind occurred with similar incidence in patients who received a single dose of oxycodone/ibuprofen (16–41%), oxycodone 5mg (27–44%), ibuprofen 400mg (11–42%) or placebo (11–55%).[33,45] No serious adverse events that occurred after a single dose of oxycodone/ibuprofen were assessed by investigators to be drug related,[33,44,45] and most (52%) adverse events that occurred with multiple doses of oxycodone/ibuprofen were mild in severity.[54] The tolerability profile of oxycodone/ibuprofen in elderly patients (aged ≥65 years) in clinical trials was similar to that observed in patients aged <65 years.[12]

Nausea, somnolence and dizziness were the treatment-related adverse events that occurred most frequently after a single dose (figure 1)[12] or multiple doses of oxycodone/ibuprofen;[12,54] nausea, somnolence and dizziness occurred in 31%, 22% and 29% of patients who received oxycodone/ibuprofen for an average of 5 days.[54] Other frequently occurring treatment-related adverse events that occurred with multiple doses of oxycodone/ibuprofen were headache (13%), pain, constipation, vomiting, asthenia, pruritus, sweating and vasodilation (all 3–7%).[54]

Fewer patients receiving oxycodone/ibuprofen than oxycodone/paracetamol 5mg/325mg experienced nausea (6.5% vs 23%; $p = 0.011$) or vomiting (3.2% vs 18%; $p < 0.009$).[44] The proportion of patients who experienced one or more adverse events in this trial was similar with oxycodone/ibuprofen and placebo (11.3% and 11.1%), but less than half that seen with oxycodone/paracetamol 5mg/325mg (27.9%) or hydrocodone/paracetamol 7.5mg/500mg (25.4%) [statistical analysis not reported].[44]

The rate of withdrawal because of adverse events in patients receiving oxycodone/ibuprofen was low (≈2%) and similar to that observed with placebo, oxycodone 5mg and ibuprofen 400mg.[33,45,54] Patients who discontinued treatment with oxycodone/ibuprofen cited nausea and/or vomiting as the rea-

sons for discontinuation,[33,45] with the exception of one patient who discontinued treatment because of headache and back pain.[45]

There was a slight decrease in blood pressure in patients who received oxycodone/ibuprofen or ibuprofen 400mg over the 6 hours after administration; systolic blood pressure decreased by 1–5mm Hg and diastolic blood pressure decreased by 4–7mm Hg.[33,54] This change was considered to reflect the analgesia experienced by patients in these treatment groups.[33] Pulse and respiratory rates were unaffected by treatment with oxycodone/ibuprofen.[54]

7. Dosage and Administration

Oxycodone/ibuprofen 5mg/400mg tablets are approved in the US for the short term (up to 7 days) management of acute, moderate-to-severe pain.[12] The recommended dose is one tablet, with a maximum of four tablets in a 24-hour period.[12] No information about the recommended interval between doses is provided in the manufacturer's prescribing information;[12] however, oxycodone/ibuprofen 5mg/400mg was administered every 6 hours in a multiple-dose study.[54]

Oxycodone/ibuprofen is contraindicated in patients with significant respiratory depression (in unmonitored settings or in the absence of resuscitative equipment), acute or severe bronchial asthma or hypercarbia, patients who have or are suspected of having paralytic ileus, and patients who have experienced asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDs.[12] Elderly patients may have an increased risk of respiratory depression with oxycodone and may be more sensitive to the gastrointestinal and renal effects of ibuprofen; caution is therefore advised when oxycodone/ibuprofen is administered to older patients. Oxycodone/ibuprofen may cause elevations of liver enzymes and renal toxicity and is not recommended for use in patients with advanced renal disease. For specific recommendations in other special patient populations and other contraindications, warnings, precautions and interactions, see the manufacturer's prescribing information.[12]

8. Place of Oxycodone/Ibuprofen in the Management of Acute, Moderate-to-Severe Pain

Acute, moderate-to-severe pain as a result of surgery or accident is experienced by approximately 25 million people in the US.[55] Although there is an obvious requirement for clinicians to provide patients with effective postoperative analgesia, surveys indicate that acute, moderate-to-severe postoperative pain is often inadequately managed and may be undertreated.[3,7,56,57] According to one survey, pain was moderate to severe in 86% of the inpatient and ambulatory surgery patients who reported pain in the 2 weeks after surgery, and patients experienced greater pain after discharge than when they were at the facility.[3] Inadequate postoperative pain management is associated with prolonged recovery time, an increased risk of clinical complications, longer hospital stays and readmissions, and increased healthcare costs.[3,5] Additionally, it is thought that adequate management of acute postoperative pain may reduce the risk of development of chronic pain.[57]

Acute pain is a complex sensation that serves as a defence mechanism for the prevention of further damage to the body.[7,33] Nociceptors are activated in response to tissue injury or inflammation and stimulate the release of neurotransmitters in the spinal cord dorsal horn neurons which transmit the signal to the brainstem, thalamus and cerebral cortex, culminating in the sensation of pain and the withdrawal reflex.[7] The release of chemicals, such as prostaglandins, from damaged cells further sensitises nociceptors to painful stimuli, resulting in peripheral sensitisation, which can lead to alterations in the structure and function of neurons.[7]

The concurrent use of analgesics with different mechanisms of action aims to improve pain relief by targeting multiple neurobiological pathways and mechanisms involved in pain sensation.[11] This approach is thought to provide better pain relief than that experienced with a single analgesic.[8,11] Indeed, additive analgesia has been demonstrated in clinical studies where patients received an opioid analgesic in combination with paracetamol, aspirin or

ibuprofen; in each case, the analgesic effect of the combination was greater than that with either component alone.[8]

Fixed-dose combination analgesic preparations provide patients with a convenient and simplified dosage regimen and the combination preparations available in the US (table VII)[58] are widely used. In 1999, over 100 million single-agent and combination preparations containing codeine derivatives (including codeine, hydrocodone and oxycodone) were dispensed in the US.[8] In a recent survey, codeine/paracetamol was the combination formulation most frequently prescribed to outpatients after surgery for the relief of postoperative pain (23%).[3]

Oxycodone/ibuprofen 5mg/400mg, the first fixed-dose combination containing oxycodone and ibuprofen, is a new addition to the range of fixed-dose combination analgesics approved in the US for the short-term management of acute, moderate-to-severe pain (section 7). It provides rapid onset, long-lasting pain relief (section 5.1.2) and most trials in the well established dental pain model (section 5.1) and in patients with pain after abdominal or pelvic surgery (section 5.2) demonstrate that a single dose of oxycodone/ibuprofen 5mg/400mg is more effective than either component administered alone. Oxycodone/ibuprofen 5mg/400mg may be particularly useful for patients with moderate-to-severe pain who are unable to take paracetamol or those who require an anti-inflammatory agent, since paracetamol would be unsuitable for such patients, and, unlike paracetamol, short-term use of oxycodone/ibuprofen 5mg/400mg is devoid of potential liver and renal toxicity.

Table VII. Oral fixed-dose combination tablet or capsule preparations containing an opioid approved in the US[58]

Preparation	Strength (mg)
Aspirin-containing combinations	
Paracetamol/codeine/aspirin	150/30/180
Hydrocodone/aspirin	5/500
Oxycodone hydrochloride/oxycodone terephthalate/aspirin	2.25/0.19/325, 5/0.38/325
Ibuprofen-containing combinations	
Hydrocodone/ibuprofen	5/200, 7.5/200
Oxycodone[a]/ibuprofen	5/400
Paracetamol (acetaminophen)-containing combinations	
Hydrocodone/paracetamol	5/325, 5/500, 7.5/325, 7.5/500, 7.5/650, 7.5/750, 10/500, 10/660, 10/750
Oxycodone[a]/paracetamol	2.5/325, 2.5/500, 5/325, 5/500, 7.5/325, 7.5/500, 10/325, 10/650
Codeine/paracetamol	15/300, 30/300, 60/300, 30/650, 60/650
Pentazocine/paracetamol	5/500
Tramadol/paracetamol	37.5/325

a Oxycodone hydrochloride.

Preliminary evidence suggests that oxycodone/ibuprofen 5mg/400mg may be more effective than some other fixed-dose combination analgesics for the relief of acute, moderate-to-severe pain. In clinical trials in patients with dental, abdominal or pelvic pain, a single dose of oxycodone/ibuprofen 5mg/400mg provided significantly better postoperative analgesia than a single dose of oxycodone/paracetamol 5mg/325mg or hydrocodone/paracetamol 7.5mg/500mg (section 5). This could be due to ibuprofen potentiating the analgesic effect of oxycodone, as has been demonstrated in an animal study (section 2), and to the relative potency of ibuprofen compared with that of paracetamol; ibuprofen 400mg provides better relief of acute postoperative dental pain than paracetamol 1000mg[59,60] or codeine/paracetamol 60mg/600mg.[61] In addition to its analgesic activity, ibuprofen has anti-inflammatory properties (section 2) which are not observed with therapeutic concentrations of paracetamol.[8]

Ibuprofen 400mg provided better analgesia than aspirin 650mg and codeine 60mg administered alone in patients with acute postoperative dental pain;[61] further studies would be useful to determine whether oxycodone/ibuprofen 5mg/400mg is more effective than fixed-dose combination analgesics containing aspirin or codeine. Similarly, it would be interesting to compare the efficacy of oxycodone/ibuprofen 5mg/400mg and hydrocodone/ibuprofen 7.5mg/200mg since the hydrocodone/ibuprofen 7.5mg/200mg fixed-dose combination provides better analgesia than either component alone in women with postoperative pain after abdominal or gynaecological surgery.[62]

Although most studies investigating the efficacy of oxycodone/ibuprofen 5mg/400mg have been conducted using the dental pain model, this is a well established model for the evaluation of analgesic efficacy for acute pain.[48] A recent analysis (available as a poster only) found that results from the dental model may be applied to other models of acute pain.[63]

A purported advantage of fixed-dose combination analgesics is that they confer fewer dose-related adverse effects than if the components were administered individually, because of the reduced dose of each component in the combination.[11] Oxycodone/ibuprofen 5mg/400mg contains a relatively low dose of oxycodone; immediate-release oxycodone tablets available in the US contain oxycodone 5–30mg.[22,58] The most frequent adverse effects that occurred with oxycodone/ibuprofen 5mg/400mg in clinical trials were opioid related (nausea, somnolence and dizziness; section 6), and the higher incidence of opioid-related adverse effects after administration of multiple doses of oxycodone/ibuprofen 5mg/400mg (section 6) probably reflects the increased oxycodone plasma concentration that is observed after repeated doses of oxycodone/ibuprofen 5mg/400mg (section 3.3). However, even after multiple doses of oxycodone/ibuprofen 5mg/400mg, these events were usually of mild severity, and there were no serious opioid-related adverse events, such as respiratory or circulatory depression, after administration of single or multiple doses.

Nausea and vomiting were significantly less frequent with oxycodone/ibuprofen 5mg/400mg than with oxycodone/paracetamol 5mg/325mg.[44] This could be due to the inhibition of central prostaglandin synthesis by ibuprofen (section 2) and a subsequent suppression of oxycodone-related nausea and vomiting.[44,45] Further studies would be useful to determine the comparative tolerability of oxycodone/ibuprofen 5mg/400mg versus other fixed-dose combination analgesics.

Ibuprofen appears to account for only a small proportion of the adverse effects associated with the use of oxycodone/ibuprofen 5mg/400mg. Aside from nausea, there was a notable absence of ibuprofen-related adverse effects such as epigastric pain and heartburn[52] in clinical trials. This may be because oxycodone/ibuprofen 5mg/400mg contains a relatively low dose of ibuprofen and is used only for short-term pain relief; many ibuprofen-related adverse effects are more common with long-term use or with higher doses of ibuprofen.[30] Clinicians must be aware that patients could potentially increase the dose of ibuprofen by taking an over-the-counter ibuprofen preparation in conjunction with oxycodone/ibuprofen 5mg/400mg, thus increasing the possibility of ibuprofen-related adverse effects.

Because oxycodone/ibuprofen 5mg/400mg is indicated for only the short-term relief of pain (maximum 7 days; section 7) it is not expected to produce any of the serious adverse effects typically associated with the long-term use of NSAIDs or tolerance or physical dependence associated with long-term (2–3 weeks), continuous use of opioids.[30] However, there are widespread misconceptions among patients about the addictive nature of opioid analgesics, which may lead to low compliance and could explain why postoperative analgesia is often inadequately managed.[3] Patients who are prescribed oxycodone/ibuprofen 5mg/400mg require education about the low risk of addiction with this combination, to ensure compliance and sufficient management of acute pain.

The cost of treatment may influence which combination analgesic is prescribed. Currently there are no data available on the costs associated with oxycodone/ibuprofen 5mg/400mg; pharmacoeconomic studies would be useful to determine its cost effectiveness versus other fixed-dose combination preparations.

In conclusion, oxycodone/ibuprofen 5mg/400mg is a useful addition to the range of oral analgesics available for the relief of acute, moderate-to-severe pain. A single dose provided better analgesia than low-dose oxycodone or ibuprofen alone in most trials and this combination appears to be more effective than some other fixed-dose combination analgesics. It is generally well tolerated after single or multiple doses, and short-term use of oxycodone/ibuprofen 5mg/400mg is not expected to produce

any of the serious adverse effects typically associated with the long-term use of opioids or NSAIDs. Thus, oxycodone/ibuprofen 5mg/400mg is a convenient, effective treatment option for the short-term management of acute, moderate-to-severe pain.

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Correspondence: *Vicki Oldfield*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz