Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

Expert Opinion

informa
healthcare

The pharmacokinetics of a long-acting OROS hydromorphone formulation

J Turgeon†, R Gröning, G Sathyan, J Thipphawong & U Richarz
†*CRCHUM, Centre Hospitalier de l'Université de Montréal, Hôtel-Dieu, Masson Pavilion, 3850 Saint-Urbain Street, Room 8-109, Montreal, Quebec H2W 1T7, Canada*

Importance of the field: New formulations of opiods can provide round-the-clock pain relief to improve pain management and quality of life for patients with chronic pain.

Areas covered in this review: Information and comments on the pharmacokinetic processes associated with a new once-daily formulation of the potent opiod hydromorphone.

What the reader will gain: This review presents an overview of data from several small pharmacokinetic studies to gain a better perspective on the pharmacokinetic properties of a new long-acting formulation of hydromorphone.

Take home message: The development of advanced oral formulation that deliver analgesic drugs over an extended period provides new solutions to improve pain management and quality of life for patients with chronic pain.

Keywords: chronic pain, once-daily dosing, OROS® hydromorphone, OROS® Push-Pull™ delivery system, pharmacokinetics

Expert Opin. Drug Deliv. (2010) 7(1):137-144

1. Introduction

Chronic pain is associated with several diseases, including cancer, chronic low back pain and osteoarthritis (OA) [1]. The prevalence of chronic pain in several developed countries was the subject of a recent systematic review [2]. In 4 studies (3 studies in the general population and 1 study of patients in primary care) that used the International Association for the Study of Pain (IASP) definition for chronic pain, the prevalence of pain > 3 months' duration ranged from 11.5 to 55.2% [2]. A recent study of the general population in 15 European countries and Israel estimated that the point prevalence of chronic non-malignant pain ranged from 11 to 30% [3]. In this study, individuals were considered to have chronic pain if they had pain lasting > 6 months, had experienced pain during the last month and several times during the last week, and rated their last experienced pain at ≥ 5 on a numeric rating scale ranging from 1 (no pain) to 10 (the worst pain imaginable) [3]. Nearly 50% of individuals with chronic severe pain believe that they do not have their pain under control [4].

The primary goals of chronic pain management are pain relief and restoration of function [5]. Adequate analgesia must be balanced with treatment-related adverse effects [6,7]. The WHO pain ladder for facilitating the management of cancer pain is commonly used when selecting medication to treat chronic pain, regardless of the underlying cause [8]. Guidelines on the use of opioids for chronic pain recommend the use of controlled release formulations and scheduled regimens [9-11].

The selection of a strong opioid should be individualised for each patient. Factors that should be assessed include pain intensity, response to previous therapy, presence of coexisting diseases (e.g., renal or hepatic dysfunction), pharmacokinetic and formulation considerations, patient convenience and the ease of titration to achieve

10.1517/17425240903386658 © 2010 Informa UK Ltd ISSN 1742-5247
All rights reserved: reproduction in whole or in part not permitted

RIGHTSLINK

Article highlights.

- OROS system releases hydromorphone at a controlled rate within the recommended 24-hour dosing interval resulting in sustained plasma hydromorphone concentrations.
- The pharmacokinetic profile of OROS hydromorphone shows dose proportionality between 8-64 mg.
- Food does not change exposure to hydromorphone when delivered by the OROS system.
- Alcohol does not change exposure to hydromorphone (no dose-dumping effect) when delivered by the OROS system.
- The OROS hydromorphone system suggest a very good safety and tolerability profile.

This box summarises key points contained in the article.

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

satisfactory analgesia [12-14]. The need for multiple daily doses of oral opioids may be associated with inconvenience for patients and poor adherence to therapy, resulting in inadequate analgesia and diminished quality of life [15]. An alternative approach to provide round-the-clock pain relief is to use long-acting oral opioid formulations [6]. An ideal round-the-clock medication should prevent return to baseline pain; supplemental doses of short-acting opioids can then be used for episodic pain (incident pain, end-of-dose pain and breakthrough pain) [16]. Long-acting opioid formulations available at present may not provide analgesia for the recommended dosing interval, and some patients take more doses than recommended in the manufacturer's prescribing information [17,18].

1.1 OROS® Push-Pull™ delivery system

The OROS® Push-Pull™ (PP) (ALZA, Vacaville, CA) osmotic oral delivery system is an active system that uses an osmotic pump to deliver the drug for up to 24 h (**Figure 1**). It can be used for a range of compounds, including both highly soluble and poorly soluble drugs, and can be adapted to provide the desired plasma profile of the active agent – by means of constant (zero order), pulsed, or patterned delivery – thereby optimising the drug's therapeutic efficacy. The system comprises a semi-rigid, non-dissolvable, rate-controlling membrane enclosing a layered core that contains active drug and excipients (the 'pull' layer) and swelling polymers (the 'push' layer). A laser-drilled hole in the outer shell, which encloses the system, serves as the delivery orifice. An osmotic gradient across the semipermeable membrane forms the driving force for fluid to enter the layered core. Both layers are osmotically active; fluid moving into the system causes the drug to go into solution (if hydrophilic) or suspension (if lipophilic) and causes the push layer to expand and displace the drug solution or suspension, resulting in drug release. Therefore, drug is released through the orifice at the rate at which fluid enters the system [19,20].

The OROS PP osmotic delivery system has been used for several sustained release formulations, including extended release nifedipine, verapamil, glipizide, doxazosin, oxybutynin, methylphenidate hydrochloride and paliperidone [21,22].

1.2 OROS hydromorphone

Jurnista™ (Janssen Pharmaceutica NV, Beerse, Belgium) is an OROS hydromorphone formulation that utilises OROS PP osmotic technology to control the delivery of hydromorphone. Hydromorphone is hydrogenated ketone analogue of morphine. It has low protein binding and is metabolised through multiple pathways, the main one being glucuronidation. As it is not metabolised by the cytochrome P450 (CYP450) pathway, it is not subject to any genetic variability or drug–drug interactions involving the CYP450 system, unlike other opioids such as oxycodone and codeine, but similar to oxymorphone (another 6-keto opioid) and close to tapentadol, which becomes mainly glucuronidated. A close relationship between analgesic effect and plasma concentration has been described for hydromorphone [23]. Once-daily administration of OROS hydromorphone provides analgesic efficacy with reduced peak-trough fluctuations [19].

In Europe, OROS hydromorphone is indicated for the treatment of moderate to severe pain that needs continuous treatment, and is now available in 5 strengths: 4, 8, 16, 32 and 64 mg [19]. Not all dosage strengths may be available in all countries.

2. Pharmacokinetic profile of OROS hydromorphone

2.1 *In vitro* studies

The *in vitro* release rate of hydromorphone from OROS hydromorphone is independent of pH and agitation rate. **Figure 2** shows the release rate of hydromorphone from the 16 mg OROS hydromorphone tablet in different media over 24 h. **Figure 3** shows that mechanical agitation does not influence the release rate of hydromorphone from the 16 mg OROS hydromorphone tablet. In these *in vitro* experiments, release rate was measured using the United States Pharmacopeia (USP) II (paddle method) dissolution apparatus.

2.2 Pharmacokinetics in healthy volunteers

Most of the OROS hydromorphone pharmacokinetic studies were done with a naltrexone block to antagonise the effects of hydromorphone. A study in healthy volunteers showed that OROS hydromorphone releases hydromorphone at a controlled rate within the recommended 24-h dosing interval (beginning ~ 2 h after administration), resulting in sustained plasma hydromorphone concentrations [24]. The hydromorphone content of the OROS hydromorphone system is released constantly during transit through the gastrointestinal (GI) tract, including the lower GI tract [19]. The rate of release of hydromorphone is independent of pH or varying motility of the GI tract [20]; therefore, 'dose dumping' is unlikely to occur with OROS hydromorphone. In situations where GI transit is prolonged (e.g., constipation), the entire drug content is released over 24 h, as designed, and even if the previous tablet has not been excreted from the body there is no risk of too much drug absorption when the next dose is taken [20].

RIGHTSLINK

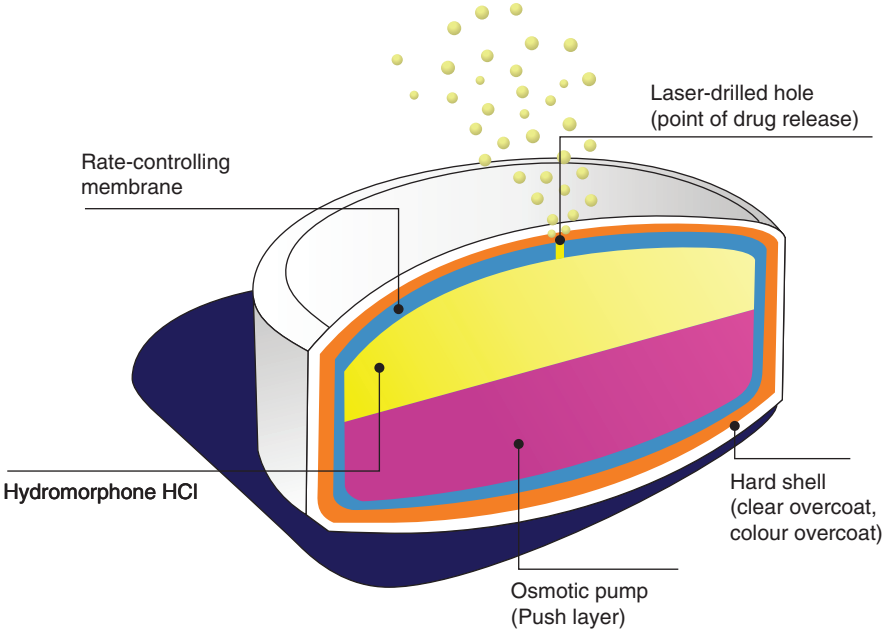

Figure 1. Cross-section of the OROS Push-Pull (ALZA, Vacaville, CA) osmotic oral delivery system.

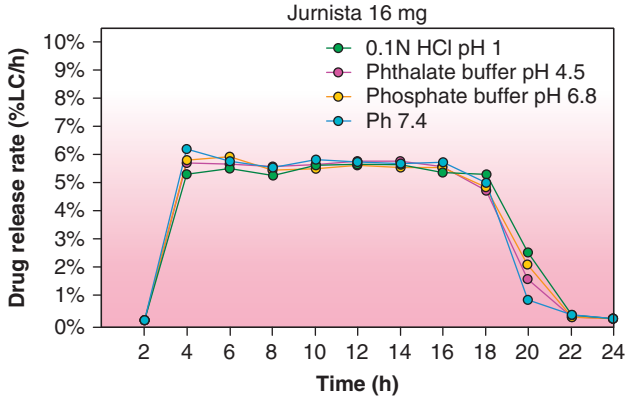

Figure 2. *In vitro* release rate of hydromorphone from OROS hydromorphone; the release is independent of pH.
LC: Label claim.

Diarrhoea does not have a negative impact on the efficacy of OROS hydromorphone in most patients, as long as GI transit time allows delivery of the drug from the OROS formulation. The OROS PP system should not be crushed under any circumstances and is therefore not suitable for patients with a percutaneous endoscopic gastrostomy tube or in any patients with prior intestinal surgery [25]. Clinical conditions or medicinal products that cause a sudden and significant shortening of GI transit time, resulting in diarrhoea (e.g., overuse of laxatives or gastroenteritis), may result in decreased hydromorphone absorption and may potentially lead to withdrawal syndrome in some patients. The pharmacokinetics and pharmacodynamics of OROS hydromorphone were initially assessed in a randomised, three-stage (six-session), placebo-controlled crossover study [23,24]. Twelve healthy volunteers received hydromorphone 8 mg intravenously (i.v.) in stage 1, 8 mg immediate release (IR) orally in stage 2, and 8, 16 and 32 mg OROS hydromorphone or placebo orally in stage 3. **Figure 4** shows the hydromorphone concentration–time profile for 8 mg IR and 8, 16 and 32 mg OROS hydromorphone. The pharmacokinetic results are summarised in **Table 1**. After administration of single doses of 8, 16 or 32 mg of OROS hydromorphone, maximum plasma concentrations of hydromorphone (C_{max}) were achieved after a median of 12.0 – 16.5 h, compared with < 1 h after administration of 8 mg IR hydromorphone [23]. The mean absolute bioavailability of hydromorphone from OROS hydromorphone was 24, 23 and 22% for the 8, 16 and 32 mg doses, respectively, and was marginally greater than the mean absolute bioavailability from the IR formulation (19%). The bioavailability of hydromorphone from OROS hydromorphone relative to IR hydromorphone was 121 – 135%, which suggested a marginally higher extent of absorption compared with the IR formulation. Exposure to hydromorphone, based on estimates of the area under the concentration–time curve (AUC) and C_{max}, was proportional to the administered dose of OROS hydromorphone over the 8 – 32 mg dose range studied [24].

In an open-label, randomised, crossover, multiple-dose study IR hydromorphone (4 mg every 6 h) was compared with once-daily OROS hydromorphone (16 mg) in 18 healthy subjects [20]. **Figure 5** shows steady-state plasma hydromorphone concentration–time curves for IR hydromorphone and OROS hydromorphone. Steady-state concentrations of

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

RIGHTSLINK

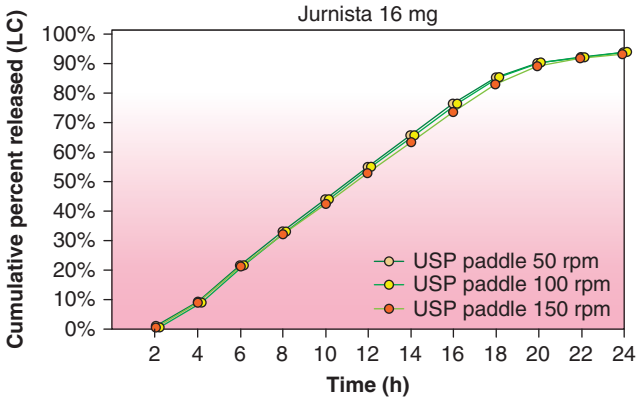

Figure 3. Cumulative *in vitro* release of hydromorphone from OROS hydromorphone; the release is independent of agitation rate.

LC: Label claim; USP: United States Pharmacopeia.

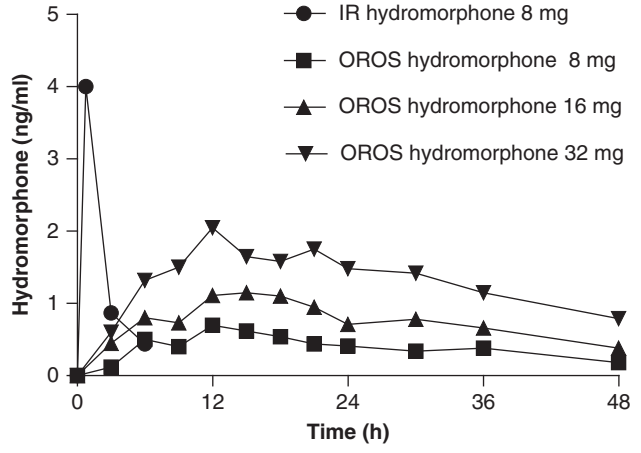

Figure 4. Mean hydromorphone concentration–time curves for immediate release hydromorphone and OROS hydromorphone.

IR: Immediate release.

hydromorphone were achieved after 48 h of OROS hydromorphone administration, and hydromorphone plasma concentrations were maintained above those following IR administration 4 times daily at the same total daily dose for each full 24-h dosing interval. Plasma concentrations of hydromorphone achieved after OROS hydromorphone administration reach ~ 80% of the peak level within 6 – 8 h, and remain elevated until ~ 24 h post-dose. Repeated administration of OROS hydromorphone is associated with a lower degree of fluctuation (DF), calculated as fluctuation = $[(C_{max,72-96h} - C_{min,72-96h})/C_{avg,72-96h}] \times 100\%$, where $C_{avg,72-96h} = (AUC_{72-96h}/24)$. The DF for the OROS hydromorphone formulation was ~ 83 (± 30)% compared with IR formulation, which was ~ 146 (± 54)% [20].

2.2.1 *Dose proportionality*

Plasma concentrations of hydromorphone after OROS hydromorphone administration are proportional across 8, 16, 32 and 64 mg doses [26]. The dose proportionality of OROS hydromorphone was assessed in an open-label, four-way crossover study in 32 healthy volunteers. Participants were randomised to receive a single dose of OROS hydromorphone 8, 16, 32 and 64 mg during each of 4 treatment periods, with a 7-day washout period between treatments. Each volunteer fasted for 10 h overnight, and was given naltrexone before, with and after OROS hydromorphone administration to antagonise opioid effects. Thirty-one volunteers completed the study. Maximum plasma hydromorphone concentrations were achieved after a median of 12 h for the 8 mg dose and ~ 16 h after administration for the 16, 32 and 64 mg doses; the dosage form release pattern did not differ significantly between the different formulations. **Figure 6** shows the dose-normalised pharmacokinetic profile of OROS hydromorphone 8, 16, 32 and 64 mg.

2.2.2 *Effects of food*

OROS hydromorphone pharmacokinetics are not significantly affected by food [27]. The effect of food on OROS hydromorphone pharmacokinetics was assessed in a study of 30 healthy volunteers. The results are summarised in **Table 2**. C_{max} and exposure (AUC_{0-t} and $AUC_{0-\infty}$) after administration with food remained within 20% of values observed under fasting conditions. The mean hydromorphone plasma concentration–time profiles following administration in the fasted and fed states were generally similar. **Table 3** summarises the statistical analysis. The 90% confidence intervals (*CIs*) (analysis of variance [ANOVA]) for the ratios of means for C_{max} under fed and fasted conditions were slightly outside the 80 – 125% limit (105.9 – 133.3%), which is not clinically significant. However, the 90% *CIs* (ANOVA) for the ratios of means for AUC_{0-t} and $AUC_{0-\infty}$ under fed and fasted conditions were within the 80 – 125% limit (84.9 – 103.7 and 81.9 – 99.4%, respectively). Therefore, exposure to hydromorphone was not significantly affected by food.

2.2.3 *Effects of alcohol*

The controlled-release property of OROS hydromorphone is maintained in the presence of alcohol [28]. A single-centre, open-label, four-treatment, four-sequence, crossover study of 2 groups of 24 healthy subjects (fasted or fed) assessed the effect of alcohol on OROS hydromorphone pharmacokinetics. Participants were randomised to receive 4 single doses of OROS hydromorphone 16 mg with a naltrexone block and 240 ml of 0, 4, 20 or 40% vol./vol. alcohol in orange juice. In both the fasted and fed groups, C_{max} was increased when OROS hydromorphone was taken with alcohol; larger differences were seen in the fasted state. In both the fasted and fed states, the upper boundaries of the 90% *CIs* for the C_{max} values of each of the 3 alcohol treatments compared with no alcohol were outside the bioequivalence limit of 125%. The greatest mean increase in

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

RIGHTSLINK

Table 1. Pharmacokinetic variables for hydromorphone after administration of OROS hydromorphone to 12 healthy volunteers.

Variable	Treatment				
	8 mg i.v.	8 mg IR tablet	8 mg OROS hydromorphone	16 mg OROS hydromorphone	32 mg OROS hydromorphone
	Mean (s.d.)				
C_{max} (ng/ml)	186 (35)	4.74 (1.76)	0.77 (0.33)	1.45 (0.43)	2.41 (0.85)
t_{max} (h)*	0.17 (0.12 – 0.17)	0.75 (0.25 – 2.00)	12.00 (6.00 – 36.00)	15.00 (6.00 – 30.08)	16.50 (9.03 – 24.00)
AUC_{0-t} (ng(min/ml))	4357 (609)	819 (283)	1089 (357)	2071 (592)	3661 (986)
$AUC_{0-\infty}$ (ng(min/ml))	NE	1078 (399)	1372 (433)	2613 (749)	4858 (1606)
AUC_{0-t}/dose (ng(min/ml))	545 (76)	102 (35)	136 (45)	129 (37)	114 (31)
$AUC_{0-\infty}$/dose (ng(min/ml))	NE	135 (50)	172 (54)	163 (47)	152 (50)
F_{rel}‡	NA	NA	1.35 (0.38)	1.28 (0.29)	1.21 (0.40)
F_{abs}§	NA	0.19 (0.05)	0.24 (0.06)	0.23 (0.06)	0.22 (0.08)

*Median (minimum–maximum).

‡F_{rel} is the relative bioavailability (estimated for OROS hydromorphone by dividing the dose normalised $AUC_{0-\infty}$ for each dose by the dose normalised $AUC_{0-\infty}$ for the IR formulation).

§F_{abs} is the absolute bioavailability (estimated for the IR formulation as AUC_{0-t} for the IR formulation divided by the AUC_{0-t} for the i.v. formulation; estimated for OROS hydromorphone as F_{abs} [IR] × F_{rel} [OROS hydromorphone]).

IR: Immediate release; i.v.: Intravenous; NA: Not applicable; NE: Not estimable for i.v.; s.d.: Standard deviation.

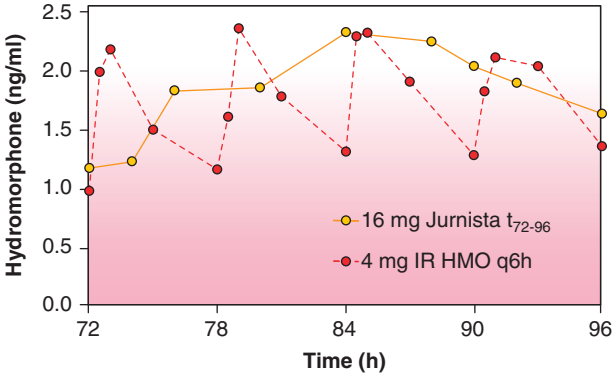

Figure 5. Steady-state plasma hydromorphone concentration–time curves for immediate release hydromorphone and 16 mg OROS hydromorphone.

IR HMO: Immediate release hydromorphone.

C_{max} observed was 1.3-fold in the fasted state and 1.1-fold in the fed state. No significant effect was seen on AUC values in the fed or fasted state; the 90% *CIs* for the AUC values of each of the 3 alcohol treatments compared with no alcohol met the bioequivalence criteria of 80 – 125%.

There was no clinically relevant uncontrolled substance release; no 'dose dumping' of hydromorphone occurred (median T_{max} was 16 h in the absence of alcohol and 12 h in the presence of alcohol). At the first measurement, 2 h after dosing, plasma hydromorphone concentrations were close to the lower limit of quantification. Plasma concentrations then rose slowly in all treatment groups. This is important in light of the suspension of the sale and marketing of an extended-release formulation of hydromorphone (Palladone XL®;Purdue Pharma PL, USA hydromorphone hydrochloride, extended-release capsules) in July 2005 owing to concerns about dose dumping with alcohol [29].

2.3 OROS hydromorphone in patients with chronic pain

An open-label, repeated dose study was done to characterise the steady-state pharmacokinetic profile of OROS hydromorphone in patients requiring daily opioid therapy for chronic pain conditions [20]. Patients stabilised on opioids were converted to OROS hydromorphone and titrated to adequate analgesia. They were then maintained on that dose for 4 – 10 days and blood samples were taken over 24 h on the last day of the study. Twenty-two patients were enrolled and 18 patients completed the study. Patients received 8, 16, 24, 40 or 48 mg OROS hydromorphone once daily.

The pharmacokinetics of hydromorphone in this study are summarised in **Table 4**. The results for mean C_{max}, C_{min} and AUC_{0-24} obtained in the 16 mg dose group were comparable to those observed for the 16 mg dose group in a previous multiple-dose study in healthy volunteers. The pharmacokinetics of hydromorphone in terms of C_{max}, C_{avg}, AUC_{0-24} and C_{min} were dose proportional over the OROS hydromorphone dose range studied.

3. Safety

The safety and tolerability of hydromorphone have been well established [30,31]. In the clinical registration trials with OROS

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

RIGHTSLINK

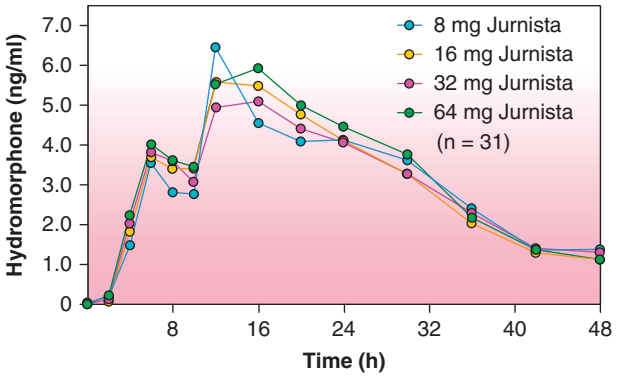

Figure 6. Plasma hydromorphone concentration profiles after administration of different doses of OROS hydromorphone, normalised to the 64 mg dose.

Table 2. Pharmacokinetic variables for hydromorphone after administration of 16 mg OROS hydromorphone to fasted and fed healthy volunteers [27].

Variable	Fasting (n = 25)	Fed (n = 27)
C_{max} (ng/ml)*	1.11 (0.206)	1.35 (0.363)
t_{max} (h)‡	16.0 (6.0 – 36.0)	12.0 (6.0 – 20.0)
AUC_{0-t} (ng(h/ml))*	31.12 (7.063)	30.20 (8.738)
$AUC_{0-\infty}$ (ng(h/ml))*	38.84 (9.566)	36.09 (10.04)

*Mean (standard deviation).
‡Median (range).
n: Number.

Table 3. ANOVA analysis of pharmacokinetic variables for hydromorphone after administration of 16 mg OROS hydromorphone to fasted and fed healthy volunteers [27].

Variable	Mean ratio (%) fed versus fasting	90% Confidence interval fed versus fasting
C_{max}	118.9	105.9, 133.3
AUC_{0-t}	93.8	84.9, 103.7
$AUC_{0-\infty}$	90.2	81.9, 99.4

hydromorphone involving 1500 patients, the most commonly reported adverse effects were nausea, constipation and vomiting [19]. In a study of patients (n = 131) treated with OROS hydromorphone for moderate-to-severe chronic low back pain, the most frequently reported adverse effects were constipation, nausea, headache and somnolence [32]. These adverse effects are commonly associated with opioid therapy and are not likely to be related to the delivery system. Most adverse effects were mild or moderate [19].

OROS hydromorphone does not contain any compounds that could act as a local irritant on the GI mucosa, such as potassium chloride, which was used several years ago in OROS formulations with other compounds. OROS hydromorphone should not be used in patients who have had surgical procedures and/or underlying disease that would result in narrowing of the gut or 'blind loops' of the gut. The OROS hydromorphone tablet is non-deformable and does not change in shape appreciably in the GI tract. The size of the system ranges from 7 to 9.5 mm in diameter. There have been very rare reports of obstructive symptoms in patients with known strictures in association with ingestion of medicinal products in non-deformable controlled release formulations containing other active ingredients [25]. This has not been observed with OROS hydromorphone.

Treatment with opioids is associated with the potential risk of drug abuse, which may result in overdose or death. In a study of healthy adult volunteers with sporadic prescription opioid abuse the relative abuse liability of oral short-acting oxycodone, hydrocodone, and hydromorphone were similar [33]. The abuse liability of OROS hydromorphone has been evaluated in a double-blind, placebo-controlled randomised, two-part, crossover study in subjects with a history of recreational opioid use [34]. Compared with 8 mg immediate release hydromorphone, OROS hydromorphone in doses ranging from 16 to 64 mg had delayed onset of positive effects and prominent bad effects, suggesting that this formulation may have lower abuse potential.

4. Conclusion

Patients with chronic pain often require around-the-clock pain relief. The development of advanced oral formulations that deliver analgesic drugs over an extended period, reducing the need for multiple daily dosing, has improved pain management and quality of life for patients with chronic pain [35].

5. Expert opinion

The OROS PP osmotic delivery system provides several important advantages over other systems for the delivery of opioid therapy in patients with chronic pain. The delivery rate is dependent on the rate-controlling membrane properties. Where other systems that deliver opioids (SODAS®, Elan Drug Technologies, Ireland; Contin®, Purdue Pharma PL, USA; AcroContin® , Purdue Pharma PL, USA and TIMERx®, Penwest Pharmaceuticals Co, USA) rely on passive processes [14, 35-37], the PP system allows effective drug delivery and analgesia with reduced peak–trough fluctuation, permitting just once-daily dosing. Clinically, less fluctuation should minimise the risk of breakthrough pain and adverse effects associated with plasma levels that are outside the therapeutic range. Once-daily dosing should improve compliance compared with formulations requiring more frequent administration. A recent review of 76 studies that utilised electronic monitoring to determine compliance with drug therapy demonstrated that compliance declined

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

RIGHTSLINK

Table 4. Pharmacokinetic variables for hydromorphone after administration of OROS hydromorphone to patients with chronic pain conditions.

Variable	Hydromorphone dose			
	8 mg (n = 6) Mean (s.d.)	16 mg (n = 5)	24 mg (n = 2)	48 mg (n = 1)
C_{max} (ng/ml)	1.27 (0.5)	2.93 (0.60)	3.43 (0.21)	7.40 (NA)
t_{max} (h)*	7.94 (0.00 – 15.00)	12.00 (0.00 – 14.97)	5.91 (5.90 – 5.92)	6.00 (NA)
C_{min} (ng/ml)	0.52 (0.29)	1.25 (0.31)	1.35 (0.12)	3.82 (NA)
t_{min} (h)	7.51 (6.52)	10.24 (10.60)	18.05 (4.42)	0 (NA)
C_{avg} (ng/ml)	0.81 (0.35)	1.92 (0.44)	2.13 (0.11)	5.29 (NA)
DF (%)‡	114.41 (89.84)	89.08 (16.42)	97.64 (0.90)	67.65 (NA)
AUC_{0-24} (ng(h/ml))	19.52 (8.31)	46.05 (10.61)	51.14 (2.56)	127.00 (NA)

*Median (minimum–maximum).
‡DF at steady-state = $(C_{max} - C_{min}/C_{avg}) \times 100\%$.
DF: Degree of fluctuation; n: Number; NA: Not applicable; s.d.: Standard deviation.

with increasing number of daily doses ($p < 0.001$); compliance was greatest with once-daily therapy (79%) [38]. Drug release from the OROS PP delivery system is not affected by pH or motility of the GI tract and drug absorption is similar in the presence and absence of food. The controlled-release property of the formulation is maintained in the presence of alcohol, with no dose-dumping observed. However, concomitant use of alcohol should be avoided because alcohol increases the C_{max} and the sedative effects of hydromorphone. The pharmacokinetic profile of OROS hydromorphone provides sustained pain relief over 24 h, which may be beneficial for patients with chronic pain who prefer the convenience of once-daily administration.

Acknowledgements

The authors thank M Lee for preparing the first draft of the manuscript on behalf of Janssen-Cilag AG in accordance with the European Medical Writers Association guidelines.

Declaration of interest

This review was funded by Janssen-Cilag Medical Affairs EMEA, a division of Janssen Pharmaceutica NV, Beerse, Belgium. J Thipphawong and U Richarz are employees of Johnson and Johnson PRD. G Sathyan is a former employee of Johnson and Johnson and a Johnson and Johnson stockholder.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. American Pain Society. Pain: current understanding of assessment, management and treatments. Available from: http://www.ampainsoc.org/ce/enduring.htm [Accessed 18 December 2007]
2. Harstall C, Ospina M. How prevalent is chronic pain? Pain Clin Updat 2003;11(2). Available from: http://www.iasp-pain.org/AM/Template.cfm?Section=Clinical_Updates&Template=/TaggedPage/TaggedPageDisplay.cfm&TPLID=5&ContentID=1566 [Accessed 18 December 2007]
3. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10(4):287-333
4. Chronic Pain in America: Roadblocks to Relief, a study conducted by Roper Starch Worldwide for American Academy of Pain Medicine, American Pain Society and Janssen Pharmaceutica, 1999 Available from: http://www.ampainsoc.org/links/roadblocks/ [Accessed 18 December 2007]
5. Argoff CE. Pharmacologic management of chronic pain. J Am Osteopath Assoc 2002;102(9 suppl 3):S21-7
6. Ballantyne JC. Chronic pain following treatment for cancer: the role of opioids. Oncologist 2003;8(6):567-75
7. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. Am J Ther 2001;8(3):181-6
8. World Health Organization. WHO's pain ladder. Available from: http://www.who.int/cancer/palliative/painladder/en/ [Accessed 18 December 2007]
9. AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc 2002;50:S205-24
10. Jovey RD, Ennis J, Gardner-Nix J, et al. Canadian Pain Society. Use of opioid analgesics for the treatment of chronic noncancer pain–a consensus statement and guidelines from the Canadian Pain Society, 2002. Pain Res Manag 2003;8(Suppl A):3Ã-28A
11. Kalso E, Allan L, Dellemijn PL, et al. Recommendations for using opioids in chronic non-cancer pain. Eur J Pain 2003;7:381-6
12. American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain, 5th edition. Glenview, IL: APS, 2003
13. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. Drugs 1996;51(5):713-37

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/04/12
For personal use only.

14. Gourlay GK. Sustained relief of chronic pain. Pharmacokinetics of sustained release morphine. Clin Pharmacokinet 1998;35(3):173-90

15. Ferrell B, Wisdom C, Wenzl C, Brown J. Effects of controlled-released morphine on quality of life for cancer pain. Oncol Nurs Forum 1989;16(4):521-6

16. Colluzi PH. Cancer pain management: newer perspectives on opioids and episodic pain. Am J Hosp Palliat Care 1998;15(1):13-22

17. Ackerman SJ, Mordin M, Reblando J, et al. Patient-reported utilization patterns of fentanyl transdermal system and oxycodone hydrochloride controlled-release among patients with chronic nonmalignant pain. J Manag Care Pharm 2003;9(3):223-31

18. Gallagher RM, Welz-Bosna M, Gammaitoni A. Assessment of dosing frequency of sustained-release opioid preparations in patients with chronic nonmalignant pain. Pain Med 2007;8(1):71-4

19. Jurnista™ monograph, Janssen-Cilag; 2006

20. Gupta S, Sathyan G. Providing constant analgesia with OROS hydromorphone. J Pain Symptom Manage 2007; 33(2S):S19-24

•• **A review of OROS hydromorphone.**

21. Swanson J, Gupta S, Lam A, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. Arch Gen Psychiatry 2003;60:204-11

22. Conley R, Gupta SK, Sathyan G. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form. Curr Med Res Opin 2006;22(10):1879-92

•• **A review of OROS technology.**

23. Angst MS, Drover DR, Lötsch J, et al. Pharmacodynamics of orally administered sustained-release hydromorphone in humans. Anesthesiology 2001;94:63-73

24. Drover DR, Angst MS, Valle M, et al. Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. Anesthesiology 2002;97:827-36

25. Bass DM, Prevo M, Waxman DS. Gastrointestinal safety of an extended-release, nondeformable, oral dosage form (OROS): a retrospective study. Drug Saf 2002;25(14):1021-33

26. Sathyan G, Xu E, Thipphawong J, Gupta SK. Pharmacokinetic investigation of dose proportionality with a 24-hour controlled-release formulation of hydromorphone. BMC Clin Pharmacol 2007;7:3

27. Sathyan G, Xu E, Thipphawong J, Gupta S. Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence and absence of food. BMC Clin Pharmacol 2007;7:2

28. Sathyan G, Sivakumar K, Thipphawong J. Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence of alcohol. Curr Med Res Opin 2008;24(1):297-305

29. FDA Public Health Advisory, 07/13/2005Available from: http://www.fda.gov/cder/drug/advisory/palladone.htm [Accessed 9 October 2008]

30. Bolay H, Moskowitz MA. Mechanisms of pain modulation in chronic syndromes. Neurology 2002;59(5 suppl 2):S2S7

31. Resine T, Pasternak G. Opioid analgesics and antagonists. In: Goodman & Gilmans the pharmacological basis of therapeutics, 9th edition. New York: McGraw-Hill; 1995. p. 521-55

32. Wallace M, Skowronski R, Khanna S, et al. Efficacy and safety evaluation of once-daily OROS hydromorphone in patients with chronic low back pain: a pilot open-label study (DO-127). Curr Med Res Opin 2007;23(5):981-9

33. Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR Jr. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend 2008;98(3);191-202

34. Shram MJ, Thipphawong J, Romach M, Sellers EM. Assessing the abuse potential of an oral osmotic-controlled extended release (OROS) hydromorphone compared to immediate release hydromorphone. Poster presented at the 28th Annual Scientific Meeting of the American Pain Society, May 6–9, 2009; San Diego, California

35. Miller DA, Dinunzio JC, Williams RO III. Advanced formulation design: improving drug therapies for the management of severe and chronic pain. Drug Dev Ind Pharm 2008;34(2):117-33

36. Gabrail NY, Dvergsten C, Ahdieh H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: a randomized controlled study. Curr Med Res Opin 2004;20:911-18

37. Reder RF. Opioid formulations: tailoring to the needs in chronic pain. Eur J Pain 2001;5(Suppl A):109-11

38. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296-310

Affiliation

J Turgeon[†1] BPharm, PhD, R Gröning[2] MD, G Sathyan[3,4] PhD, J Thipphawong[5] MD & U Richarz[6] MD
[†]Author for correspondence
[1]Research Director CRCHUM,
Centre Hospitalier de l'Université de Montréal,
Hôtel-Dieu, Masson Pavilion,
3850 Saint-Urbain Street, Room 8-109,
Montreal, Quebec H2W 1T7, Canada
Tel: +514 890 8044; Fax: +514 412 7186;
E-mail: Jacques.turgeon.chum@ssss.gouv.qc.ca
[2]Institut für Pharmazeutische Technologie und Biopharmazie,
D-48149 Münster, Germany
[3]Adamas India Pharmaceuticals Private Limited,
Bangalore, India
[4]ALZA Corporation,
Mountain View, CA 94039, USA
[5]Johnson and Johnson PRD,
Fremont, CA 94043, USA
[6]Global Medical Affairs,
Johnson & Johnson
Pharmaceutical Services,
LLC, Sihlbruggstrasse 111,
6340 Baar, Switzerland

RIGHTSLINK