Pain Medicine

PAIN MEDICINE
Volume 10 • Number S1 • 2009

Enteral Controlled-Release Opioid Delivery Systems

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ABSTRACT

Multiple formulations exist to provide enteral controlled-release (CR) opioid delivery. An appreciation of these various delivery systems may provide clinicians with the knowledge to feel comfortable utilizing multiple different opioid CR formulations in their practices in efforts to optimize patient analgesia while minimizing adverse effects.

Key Words. Opioids; Enteral Controlled-Release Opioid Delivery Systems; Alcohol; Oxymorphone; ECRO

Introduction

There are multiple routes/delivery systems (available and developed but not yet clinically available) that provide a controlled release (CR) of opioid over a period of 12 hours or longer including: enteral delivery systems, transdermal delivery systems (topical CR opioid), implanted systemic delivery systems (parenteral CR opioid), and spinal (e.g., epidural) (spinal CR opioid) delivery formulations (Table 1). The CR opioid delivery system, which currently features the largest selection of different opioids, is the enteral controlled-release opioid (ECRO) delivery systems (enteral CR tablets or capsules) (Table 2).

CR tablets that prolong drug delivery have one particular technical feature in common: they all have a barrier zone that restricts the free movement of drug into the lumen of the gastrointestinal (GI) tract [1].

ECROs

Multiple formulations adsorb opioid onto a hydrophilic polymer (e.g., hydroxyalkyl cellulose), which is embedded in some form of a wax or hydrophobic matrix (higher molecular weight aliphatic alcohols), granulated, and finally compressed into tablets [2]. After enteral administration, gastric fluid dissolves the tablet surface and hydrates the hydrophilic polymer to produce a gel, the formation of which is controlled by higher aliphatic alcohols. The rate of drug release from this formulation depends on the rate of diffusion of the dissolved opioid through the gel layer at the surface of the tablet. The depth of the gel layer increases over time as the gastric fluid gains access to the deeper regions of the tablet [2]. The release rate can be controlled by varying the hydrophilic polymer, the type of hydrophobic matrix, or their ratio. Variants of this approach have been used for MSContin (Purdue Frederick, Stamford, CT) and Oramorph SR (Xanodyne Pharmaceuticals, Cincinnati, OH) [2].

Alternatively, a pellet or granule can be created, composed of an inert core (e.g., a sugar) onto which a defined small dose of opioid and a polymer coat of defined porosity and thickness is sequentially sprayed [2]. Fluid in the GI tract diffuses through the outer polymer coat to dissolve the opioid after enteral administration; the nature of the inert core together with the composition and thickness of the coat combine to control the rate of dissolution. As individual pellets are essentially identical, the different dosage strengths are created by packaging a certain weight of pellets into an appropriately sized capsule. Following capsule disintegration, the relatively small sized granules behave more like a liquid than larger solid particles, which may, on occasion, be retained in the stomach [2]. Other types of CR opioid delivery systems include small granular particles containing opioid which are bound together to form larger particles with a hydrophobic wax [2], or suspension formulations where opioid is

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© American Academy of Pain Medicine 1526-2375/09/$15.00/S30 S30–S38 doi:10.1111/j.1526-4637.2009.00597.x

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Table 1 Multiple routes of controlled-release opioid delivery systems

Route	Example	Opioid
TOPCRO	Duragesic®	Fentanyl
ECRO	OPANA ER®	Oxymorphone
PACRO	Chronogesic®*	Sufentanil
SPICRO	DepoDur®	Morphine

* Not clinically available.
TOPCRO = topical controlled-release opioid (consists of peridermal controlled-release opioids and and transdermal controlled-release opioids); ECRO = enteral controlled-release opioid; PACRO = parenteral controlled-release opioid; SPICRO = spinal controlled-release opioid.

attached to small beads of an ion exchange resin (for patients who had difficulty swallowing solid dosage forms), where once administered, the sodium and potassium ions present in the GI tract fluids gradually displace opioid from the resin [2].

There are substantial differences in the pharmacokinetics of opioid following the administration of the various modified-release opioid formulations. Intuitively, these differences would be expected to translate into measurable differences in opioid pharmacodynamic effects of pain relief and the incidence and severity of adverse effects. While open-label studies of efficacy have shown differences in pharmacodynamic effects, the global assessments of efficacy, and patient preference for a particular modified-release formulation, other studies using the gold standard double-blind, double-dummy crossover design have failed to replicate these findings [2].

There are three commonly used modified-release formulations of morphine (MSContin, Kadian [Alpharma Branded Products Division, Piscataway, NJ] and Avinza [King Pharmaceuticals, Inc., Bristol, TN]). Kadian and Avinza have smaller trough to peak fluctuations compared with MSContin [3,4]. This means these agents have lower maximum and higher minimum concentrations than MSContin. The clinical benefit of these pharmacokinetic differences did not correlate with higher efficacy or safety in clinical studies when Kadian or Avinza were compared with MSContin [5,6].

Although all CR products may be taken without regard to meals, they are sensitive to alterations that destroy their modified-release mechanisms. Therefore, these products should be swallowed whole (i.e., not broken, chewed, crushed, or dissolved) due to the risk of rapid opioid release and absorption of potentially fatal doses. For patients experiencing difficulty swallowing, capsule products such as Avinza and Kadian may be opened and their entire bead contents sprinkled onto

Table 2 Data on selected enteral controlled-release opioids

Product	OPANA ER	Kadian	MSContin	OxyContin	Avinza
Dosing Interval (hours)	12	24	12	12	24
Opioid	Oxymorphone	Morphine sulfate	Morphine sulfate	Oxycodone	Morphine sulfate
Dosage form	Extended-release tablets	Sustained-release capsules	Controlled-release tablets	Controlled-release tablets	Extended-release capsules
Doses (mg)	5, 7.5, 10, 15, 20, 30, 40	10, 20, 30, 50, 60, 80, 100, 200	15, 30, 60, 100*, 200*	10, 20, 40, 80*, 160*	30, 60, 90, 120
Half-life (hours)	9–11	23	5–8	0.6—initial release 6.9—prolonged release	24
Controlled-release technology	TIMERx	P-ERMS	Contin (Dual hydropolymer matrix)	AcroContin	SODAS
C_{max} (ng/mL)	0.27 (OPANA ER 5 mg single dose) 1.21 (OPANA ER 20 mg single dose)	15.6	30.5	21.4 (OxyContin 20 mg single dose)	~18.65
AUC (ng/mL)	17.81 (OPANA ER 20 mg single dose)	271	304.3	207.5 (OxyContin 20 mg single dose)	~273.25
T_{max} (hours)	3	8.6	2.5	3.2 (OxyContin 20 mg single dose)	
Time to steady state (days)	3	~2	1	1–1.5	2–3

* For use in opioid-tolerant patients only.

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applesauce immediately before administration [3,4]. The applesauce should be room temperature or cooler, and the entire amount should be consumed without chewing, followed by rinsing and swallowing with water to ensure that all beads are ingested. The prescribing information for Kadian also indicates that the entire capsule contents may be administered through a 16 French gastrostomy tube [4].

MSContin CR Morphine Tablets

MSContin (morphine sulfate CR tablets) utilizes the Contin matrix drug delivery system [7]. In matrix-type modified-release drug delivery systems, the active ingredient and retarding ingredients are uniformly distributed throughout the dosage form. The retardants control the rate of release of the active ingredient (morphine, in the case of MSContin) from the tablet matrix [8].

The Contin drug delivery system depends on two different types of retardants to control the rate of drug release. The relative proportions of these retardants assure the measured release of the active ingredient. The Contin system employs one water-insoluble and one water-soluble polymer. The retarding ingredients consist of highly polar cellulose and long-chain aliphatic alcohols.

MSContin CR tablets contain morphine sulfate in a dual-control polymer matrix (Contin) that consists of a hydrophilic polymer (hydroxypropyl methylcellulose) and a hydrophobic polymer (hydroxyethyl cellulose) [9]. To prepare these systems, the drug is blended with the hydrophilic polymer, selectively hydrated with a polar solvent, and fixed with a higher aliphatic alcohol [10]. The partition coefficients of the active ingredient with the hydrophilic and hydrophobic components of the formulation control the release of drug from the tablet [11]. The hydrophobic content is used to slow the diffusion of drug into the aqueous phase, which limits diffusion into the GI tract and absorption into the body.

The composition of the tablet matrix is such that intact passage throughout the intestinal tract is not expected [7]. Dissolution studies have shown that "ghost tablets" can exist and patients should be advised that they may pass empty matrices via colostomy or in the stool [7].

Kadian Sustained-Release (SR) Morphine Capsules

Kadian SR capsules contain morphine sulfate in identical polymer-coated, SR pellets; the product does not contain an immediate-release component

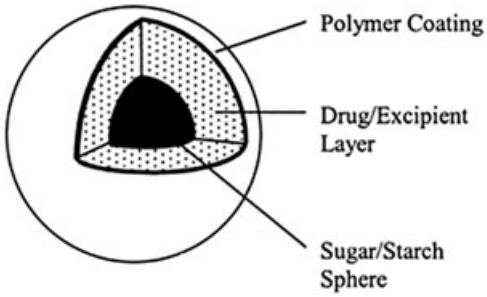

Figure 1 Representation of an extended-release bead formulation.

[4]. The pellets are similar in general structure to the ER beads in Avinza (Figure 1). However, their polymer coating consists of an insoluble ethylcellulose base along with polyethylene glycol (PEG) and a methacrylic acid copolymer. Both the PEG and methacrylic acid copolymer are water-soluble, but the water solubility of the methacrylic acid copolymer is pH-dependent. After ingestion, the hard gelatin capsule shell quickly dissolves, releasing the drug-containing pellets. In the acidic pH of the stomach, the PEG component of the polymer coating dissolves and immediately creates pores that allow GI fluid to enter the pellets and dissolve the morphine sulfate, which can then diffuse and be absorbed into the body. As only the PEG component can dissolve at that point, the pores are relatively small, limiting drug diffusion. However, this does allow for some drug to be absorbed quickly into the body. As the pellets enter and move through the intestines, the pH of the GI environment continues to increase, and the methacrylic acid copolymer begins to dissolve as the PEG continues its dissolution. This increases the number and size of the pores in the polymer coating, which increases the rate of morphine release.

Polymer-coated extended-release morphine sulfate (P-ERMS) provides 12–24 hours of pain relief [12]. P-ERMS is indicated for QD or BID dosing [4]. P-ERMS exhibits linear pharmacokinetics and its bioavailability is not affected by meals [13,14]. It has a plasma concentration-time curve that is relatively flat and smooth [14]. When compared with a 12-hour CR morphine sulfate tablet, P-ERMS exhibited a higher minimum concentration, a longer time of maximum concentration (T_{max}), and a greater time that concentration was a ≥75% of maximum concentration, an index of the control the formulation exerts over the morphine release rate [14,15].

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Avinza Extended-Release (ER) Morphine Capsules

Avinza ER capsules contain morphine sulfate in both immediate and ER beads [3]. The immediate-release component achieves plateau morphine concentrations within 30 minutes while the ER component maintains these plasma concentrations throughout the 24-hour dosing interval, which is longer than most other oral modified-release opioid products are able to achieve. The SODAS (Spherical Oral Drug Absorption System, Elan Corporation, Dublin, Ireland) is used to produce the ER component of the product. The ER beads are prepared using sugar/starch spheres upon which a drug/excipient layer is coated, followed by an ammonio-methacrylate copolymer coating.

SODAS is a multiparticulate drug delivery technology based on the production of CR uniform spherical beads of 1–2 mm in diameter. Each bead begins as a nonparallel core (which functions as a carrier), onto which a solution of active ingredient is applied. A series of subsequent coatings with timing solutions containing both soluble and insoluble polymers and other excipients combine to produce the outer rate-controlling membrane that ultimately controls release of drug from the beads. Once produced, the beads are encapsulated into a hard gelatin capsule. Combining a number of different populations of beads with varying degrees of CR may allow for tailored drug release profile. Drug is released from the beads by a process of diffusion. Within the GI tract, the soluble polymers dissolve, creating multiple pores in the outer coating of the bead, thus permitting fluid to enter the bead core and solubilize the drug. The resultant solution then diffuses out in a predetermined manner, prolonging the in vivo dissolution and absorption phases.

After administration and rapid dissolution of the hard gelatin capsule shell, the permeability of the ammonio-methacrylate copolymer coating allows GI fluid to enter the beads and solubilize the drug. The entrance of GI fluid is mediated by fumaric acid, which acts as an osmotic agent and local pH modifier within the drug/excipient layer.

As a result, drug release is independent of the pH of the surrounding GI environment. The immediate-release beads are formed by utilizing the same sugar/starch core and drug/excipient layer, without the rate-limiting polymer coating, and contain approximately 10% of the respective dose [16]. Dosing is limited to no greater than 1,600 mg/day due to fumaric acid levels that may, theoretically, result in renal toxicity; however, fumaric acid has poor oral bioavailability.

CR Oxymorphone

Oxymorphone ER is a new SR tablet formulation of oxymorphone hydrochloride developed to provide 12 hours of sustained analgesia [17]. The TIMERx technology is based on a customized, agglomerated hydrophilic complex which forms a CR matrix upon compression. The matrix consists of two polysaccharides, xanthan and locust bean gum (LBG). Interactions between these compounds in an aqueous environment form a tight gel with a slowly eroding core. As water is absorbed into the outer layers, the tablet begins to swell and gradually break down. The center core reduces slightly as some of the drug is released.

The TIMERx (Penwest Pharmaceuticals Co., Danbury, CT) molecular engine has two heterodisperse polysaccharides that self-assemble into a complex three-dimensional structure [18]. The interactions between the two polymer molecules can be engineered to allow them to become entwined, disentangled, more entangled, or dissolved with time depending on requirements or in response to physiological conditions. The keys that switch the molecular engine on and off are the London-van der Waals, hydrogen and/or ionic bonds between the two heterodisperse polysaccharides [18].

Xanthan is a heterpolysaccharide, which dissolves in water to form viscolysed or thickened solutions [1]. This thickening property of xanthan is made use of in other pharmaceutical products to prepare sugar-free syrups and results from a reversible dimerisation of xanthan molecules. In solution, one xanthan molecule associates with a second molecule by hydrogen bonding to produce a helical structure. These xanthan helices are dispersed through the solution and act to create sufficient inhibition of free movement of water molecules from the GI tract to produce the thickening observed (but there is no interlinking of separate helices) [1].

LBG is a long-chain homopolysaccharide that is physicochemically more complex than xanthan. The LBG molecule has two distinct regions, which alternate along the mannose polymer backbone. During biosynthesis, galactose residues periodically become attached roughly once in every four mannose units. The regions of LBG where successions of galactose molecules stick out

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from the mannose backbone are known as "hairy" regions. Regions of the LBG molecule that are free of galactose residues are known as "smooth" regions. The absence of galactose in the smooth regions allows two LBG molecules to become hydrogen bonded, and the existence of more than one smooth region on every LBG molecule allows several different LBG molecules to become entangled by hydrogen bonding. This produces a three-dimensional interlocking network of LBG molecules in water [1].

When LBG is mixed with xanthan, a synergistic interaction occurs, which results in the rigid helices of xanthan in solution becoming incorporated into the true gel structure of the LBG molecules. The interaction can be considered synergistic because the viscosity build that occurs when both polysaccharides are used together is significantly greater weight for weight than either material used alone. This is due to the xanthan helices forming molecularly rigid "pillars" within the LBG matrix, further stiffening the three-dimensional structure of the true gel [1]. Also, when the two polysaccharides are mixed, gel formation develops at ambient temperature [1].

In TIMERx tablets, when a molecular valve is open, the drug can pass out of that part of the gel; but when a valve is closed, drug diffusion is stopped. A valve can be considered open when the intermolecular bonding between xanthan and LBG is either at a minimum or at a maximum (e.g., over-crosslinked). The molecular valve opening and closing in TIMERx gels is controlled by the degree of crosslinking "allowed" at a given point in time. For example, a low degree of crosslinking between the polymer chains is likely to cause valves to be open, as there will be a large number of less tortuous channels in the gel. As the polymer chains crosslink, the pores become more tortuous and constricted, leading to valve closure [1]. This system is thought to help ensure reliable and steady drug release over 12 hours.

OxyContin CR Tablets

OxyContin tablets utilize the AcroContin matrix drug delivery system (2-data on file Purdue) (Purdue Pharma L.P., Stamford, CT). In matrix-type modified-release drug delivery systems, the active ingredient and retarding ingredients are uniformly distributed throughout the dosage form. The retardants control the rate of release of the active ingredient (oxycodone, in the case of OxyContin) from the tablet matrix [8].

The AcroContin drug delivery system depends on two different types of retardants to control the rate of drug release. The relative proportions of these retardants assure the measured release of the active ingredient. The two retarding ingredients are ammonio-methacrylate copolymer, a water-insoluble polymer, and stearyl alcohol, a water-insoluble wax. Both ingredients are suitable retardants for oxycodone, as oxycodone is water-soluble. The oxycodone in an OxyContin tablet is contained in a homogenous mixture of the active drug (oxycodone) and retardants, that is, there are not two separate components to a tablet (OxyContin does not contain a separate immediate-release component [7]).

After ingestion, the GI fluid dissolves the tablet coating, exposing the hydrophobic acrylic matrix. After the film coating on the tablet has dissolved, GI fluid enters the tablet matrix release of oxycodone from OxyContin, resulting in the dissolution of the entrapped oxycodone and diffusion of oxycodone through the tablet matrix. The water-insoluble matrix of the AcroContin delivery system renders the oxycodone release from the OxyContin tablets independent of surrounding pH [7].

As the matrix is hydrophobic and does not dissolve, patients should be advised that they may pass empty tablets or "ghosts" in the stool or via colostomy and that this is not a concern as the active ingredient has already been released from the tablet.

Mandema et al. [19] developed pharmacokinetic models for OxyContin and for an immediate-release oxycodone solution (IR oxycodone) based upon pharmacokinetic data from a study of healthy subjects who received single 20 mg doses of each formulation. The resulting pharmacokinetic models were then used to predict mean concentration vs time profiles for dosing of OxyContin (q12h) and immediate-release oxycodone (q6h) for 3.5 days.

Mandema et al. [19] found that the oxycodone absorption profile for OxyContin has a complex shape. Unlike oxycodone immediate-release, the shape could not be accurately described mathematically using a single exponential term (i.e., a mono-exponential function.). However, the observed absorption profile for OxyContin could be accurately described mathematically as the sum of two exponential terms (i.e., a biexponential function).

As the two exponential terms in the biexponential absorption model necessarily have different

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exponents (rate constants) whose magnitudes are directly to their respective rates, the term with the higher rate constant can be considered the "faster" term and the other the "slower" term. Further, the modeling defines the relative mathematical contributions of the two terms in the overall OxyContin absorption model, with 38% of total absorption represented by the "faster" exponential term and 62% represented by the "slower" exponential term. These proportions represent the mathematical factors that scale the contributions of the two exponential terms so that they sum to give the observed OxyContin absorption profile. The 38% and 62% values have no specific physical or functional representation within an actual OxyContin tablet. Nor is there a specific relationship between the two retardants and the two terms in the absorption model.

At the start of oxycodone absorption, the rate of absorption for immediate-release oxycodone is more than eightfold higher than the rate for OxyContin. The immediate-release oxycodone absorption model indicates that, on average, approximately 50% of the total absorption will be complete within 10 minutes after absorption begins. In contrast, the OxyContin absorption model indicates that less than 10% of the total absorption will be complete within 10 minutes after absorption begins. The modeling indicates that absorption from a dose of an immediate-release oxycodone solution will be essentially complete approximately 1.5 hours after absorption begins, at which time absorption from OxyContin is approximately 40% complete. Oxycodone absorption from OxyContin is only 75% complete at 9 hours after absorption begins and is approximately 95% complete at 24 hours. Taking broken, chewed, or crushed Oxycontin tablets and other SR products "bypasses" the ER technology of the formulation and leads to rapid release and absorption of oxycodone, which may yield blood levels of a potentially fatal dose.

Potential ECROs for the Future

OROS Hydromorphone ER Tablets

Although currently, there are no Food and Drug Administration (FDA)-approved formulations of hydromorphone available in the United States, a once-daily OROS formulation of hydromorphone (OROS hydromorphone) has been developed using OROS Push-Pull osmotic active technology (Alza Corporation, Mountain View, CA), which is designed to achieve relatively constant steady-state concentrations for 24 hours. Wallace et al. performed an open-label multicenter study of patients with chronic cancer pain who were successfully converted from opioid agonist therapy to OROS hydromorphone [20].

Alza Corporation developed the OROS (Oral Osmotic) drug delivery system. The elementary OROS osmotic pump delivery system consists of a tablet core of drug surrounded by a rate-controlling semi-permeable membrane coating that is pierced by a small (0.4 mm diameter) hole laser-drilled hole. The core table has two layers, one containing the drug (the active layer) and the other containing a polymeric osmotic agent (the push layer), which operates on the principle of osmotic pressure.

The semi-permeable membrane permits water to enter from the patient's stomach into the core tablet when the tablet is swallowed, thereby dissolving or suspending the drug. As pressure increases in the osmotic layer, it pumps the drug solution out of the delivery orifice at a constant rate of about one to two drops per hour.

Only the drug solution (not the undissolved drug) is capable of leaving through the small delivery orifice. The system is designed such that only a few drops of water are drawn into the tablet every hour. The rate of water inflow into the tablet as well as the release of drug solution from the tablet depends on an osmotic gradient between the contents of the two-layer core and the fluid in the GI tract. Potential factors that may influence the drug release rate could include the osmotic gradient between the tablet core and the GI tract, the surface area, thickness, or composition of the membrane, and/or the diameter of the drug delivery orifice.

Palladone ER Hydromorphone Capsules

Palladone (Purdue Pharma, Stamford, CT) ER capsules were launched in February 2005 and marketed to a limited number of medical practitioners [21]. The capsules were the first oral modified-release opioid product that contained hydromorphone HCl. The product used an around-the-clock matrix pellet formulation to achieve a biphasic release of drug that resulted in a relatively rapid rise to an initial peak concentration, followed by a second broad peak with therapeutic plasma concentrations maintained over the 24-hour dosing interval [22]. During product development, results indicated that consuming ethanol while taking Palladone disrupted the modified-release mechanism

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of the product and resulted in the absorption of a potentially fatal dose of hydromorphone [21]. Purdue disclosed to the FDA that peak blood concentrations increased approximately six times with the consumption of 8 oz of a 40% (80 proof) ethanol solution and approximately two times with the consumption of 8 oz of a 4% ethanol solution [23]. In July 2005, the FDA advised Purdue that the risk of alcohol interaction cannot be adequately managed with warnings alone, and, at the request of the FDA, Purdue suspended all marketing and sales of Palladone [21].

After the withdrawal of Palladone from the market, the FDA recommended that makers of other ER formulations conduct investigations to determine the risk of alcohol-induced dose-dumping, whereby alcohol interacts with the ER characteristics to yield unintended, rapid drug release in a short period of time [24,25]. In vitro studies conducted with an ER formulation of morphine sulfate (Avinza, King Pharmaceuticals, Inc., Bristol, TN) demonstrated accelerated release of morphine in buffer solutions containing ethanol. As a result, the Avinza label was revised to warn against consumption of alcohol and use of medications containing alcohol while taking the product [26,27]. Similar information was placed as a Black Box Warning for ER oxymorphone hydrochloride (OPANA ER, Endo Pharmaceuticals, Chadds Ford, PA) due to results of an in vivo study examining the effect of alcohol on the bioavailability of a single 40-mg dose in healthy fasted volunteers [28].

Although in vitro studies did not demonstrate any enhancement of release by 4%, 20%, or 40% ethanol admixtures in simulated gastric fluid (0.1 N HCl), there is an in vivo interaction of oxymorphone ER with ethanol [29]. Oxymorphone ER 40 mg was coadministered with 240 mL of 0%, 4%, 20%, and 40% aqueous ethanol solution. Mean area under curve (AUC) was not significantly affected by ethanol at any concentration, although the mean increase with 40% ethanol solution was approximately 13%. Of interest was the high degree of variability of peak drug concentration (C_{max}) during coadministration. Across all study conditions, the change in C_{max} ranged from a 50% decrease to a 270% increase. With the 40% ethanol solution, C_{max} increased by a mean of 70% (in individual subjects, by up to 270%). With the 20% solution, C_{max} increased by a mean of 3% (in individual subjects, by up to 260%). With the 4% solution, C_{max} increased by a mean of 7% (in individual subjects, by up to 110%) [29]. On the basis of these data, the manufacturer cautions against coadministration of both formulations with ethanol [29,30]. The nature of the interaction of oxymorphone ER and alcohol is unknown. In vitro dissolution studies suggest it is not caused by an ethanol-mediated deterioration of the formulation. Similar interactions have been seen with food suggesting that effects on gastric emptying or splanchnic blood flow may be contributing.

Johnson et al. [31] performed an open-label, randomized, three-way crossover study with an additional index arm, conducted among 32 healthy male volunteers, found no significant evidence of a formulation interaction between Kadian and alcohol, in vivo. The pharmacokinetics of serum morphine did not differ significantly among subjects taking Kadian with water (fasted) or with 240 mL 40% alcohol under fasted or fed conditions. Analysis of variance (ANOVA) ratios of least-squares means for in-transformed AUC_{∞} and C_{max} satisfied the criteria (90% confidence intervals within 80–125%) to declare no drug formulation interaction among the Kadian regimens dosed with alcohol compared with Kadian taken with water. There were no serious adverse events or deaths reported during the study.

Thus, the in vivo data suggest that rate and extent of absorption of morphine from Kadian dosed with alcohol under fasted or fed conditions was similar to that of Kadian given with water under fasted conditions, the ER mechanism of the Kadian formulation was not significantly affected by 40% alcohol. The FDA has reviewed data from this study, has concurred that there is no interaction between Kadian and alcohol in vivo when administered concomitantly, and has not required any changes to the package insert [32].

In a single-center, open-label, four-treatment, four-period, four-sequence, crossover study, two groups of 24 healthy subjects (fasted or fed) were randomized to receive four single doses of OROS hydromorphone 16 mg with solutions of either 0%, 4%, 20%, or 40% alcohol, and with a naltrexone block [33]. Plasma samples taken predose and at regular intervals up to 48 hours after dosing were assayed for hydromorphone concentrations; a mixed-effect ANOVA was done on log-transformed data [33]. Bioequivalence was concluded if 90% confidence intervals of treatment mean ratios were between 80% and 125% [33]. Plasma hydromorphone concentrations were slightly higher after dosing with all alcohol treat-

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ments in both the fasted and fed subject groups. Median T(max) values were between 12 and 16 hours and ranges were similar for all treatments [33]. C_{max} values increased after alcohol compared with no alcohol, with the increase slightly lower in the fed state. The greatest mean increase in C_{max} observed was 1.3-fold in the fasted state and 1.1-fold in the fed state. Confidence intervals were within 80–125% for AUC but were slightly higher for C_{max} [33]. Sathyan et al. concluded that the pharmacokinetics of once-daily OROS hydromorphone were only minimally affected by alcohol, with no dose-dumping of hydromorphone. The results indicate that the CR properties of this formulation are maintained in the presence of alcohol [33].

Traynor and colleagues found that tramadol release from Ultram ER tablets (Pricara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ) and T-long capsules was significantly increased in the presence of ethanol [34]. Conversely, a decrease in the in the rate of tramadol release was seen from Tridural ER tablets (Pricara®, Division of Ortho-McNeil-Janssen Pharmaceuticals) in the presence of alcohol.

Purdue Pharma has conducted in vitro studies of the effect of alcohol on the dissolution profile of MSContin and OxyContin tablets. These in vitro dissolution studies show that exposure to alcohol does not increase the rate at which morphine is released from MSContin tablets or at which oxycodone is released from OxyContin. Further, these in vitro dissolution studies demonstrate that the rate at which morphine is released from MSContin tablets or at which oxycodone is released from OxyContin tablets actually decreases as the concentration of alcohol is increased [7]. Therefore, Purdue Pharma has not conducted an in vivo study to assess the effect of alcohol on morphine release from MSContin tablets or OxyContin tablets in human subjects.

Other delivery system techniques (e.g., SABER™, MICRODUR™, DURIN™ [Durect Corporation, Cupertino, CA]) are being investigated for use with multiple opioids in various routes of administration. The SABER delivery system is a biodegradable drug delivery platform that can be formulated for parenteral or enteral routes of administration, which appears to be especially well suited for small-molecule and protein delivery. After a single injection, an active agent may conceivably achieve a duration of action of up to 3 months (small molecules) or 30 days (proteins).

Summary

Opioids can currently be enterally administered in 12-hour-24-hour CR formulations. Furthermore, the future list of ECRO formulations which may potentially be approved by the FDA continues to grow (e.g., a twice-daily ER hydrocodone/acetaminophen formulation and multiple CR hydromorphone formulations). An understanding of the pharmacokinetics/pharmacodynamics of these CR opioid formulations, in concert with an appreciation of the differences in their delivery mechanisms and nuances of how they could interact with alcohol or other substances, may facilitate the optimal use of CR enteral opioids for patients with significant persistent pain.

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