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Gastrointestinal Safety of an Extended-Release, Nondeformable, Oral Dosage Form (OROS®)[1]

A Retrospective Study

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Abstract

Background: The OROS® osmotic (OSM) dosage form optimises extended-release oral administration by controlling the rate of drug release for a predetermined time, providing constant, patterned, or pulsed delivery profiles. OSM products include prescription medications for urology, CNS, and cardiovascular indications, as well as over-the-counter nasal/sinus congestion medications.

Methods: This retrospective study examines US gastrointestinal (GI) safety data for the OROS® dosage form following nearly two decades of use. Although GI injury and obstruction are known effects of oral medications, some reports have suggested that extended-release products pose a greater risk of GI injury and obstruction than other oral dosage forms. Products incorporating OROS® technology are being prescribed to an expanding range of patients; a review of the GI safety data for this dosage form thus seemed timely and appropriate. US safety information was obtained from three sources: (i) English language literature published from 1982 until June 1, 2000 from five major biomedical databases; (ii) postmarketing safety reports from January 1, 1983 until June 1, 2000 available through the Freedom of Information Act; and (iii) commercial safety information obtained directly from ALZA Corporation's in-house safety database for those OSM products for which ALZA has reporting responsibility. US distribution data from IMS National Prescription Audit™ Plus data were used to estimate cumulative product distribution totals. These totals were combined with numbers of unique GI events to determine the estimated frequency of events.

Results: Nearly 13 billion OSM tablets are estimated to have been distributed in the US. The incidence of all clinically significant GI adverse events for OSM products (including intestinal, gastric, and oesophageal irritation, injury, and obstruction) reported in the US was approximately one case in >76 million tablets distributed. The majority (78%; estimated incidence: one case in 29 million tablets) of cases were reported in patients taking Procardia XL® (nifedipine).

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

Oesophageal and lower GI obstruction were reported primarily in patients with pre-existing abnormalities or disease of the GI tract. Among paediatric patients, one obstruction was reported in an estimated 37.7 million tablets distributed. Reports of GI irritation associated with OSM products were consistent with known effects of the same drug substances in other dosage forms.

Conclusion: A review of long-term safety experience with products using OSM controlled-release technology yields a low incidence of clinically significant GI events. Properly prescribed, extended-release products provide substantial therapeutic and convenience benefits without additional risk.

The aim of this study was to analyse the gastrointestinal (GI) safety data available for the OROS® controlled-release drug delivery products produced by ALZA Corporation, following nearly two decades of use in the US. Although GI injury and obstruction are known effects of oral medications, some reports have suggested that extended-release products pose a greater risk of injury and obstruction than other oral dosage forms. Since products incorporating OROS® technology provide controlled delivery of a variety of drugs in an expanding range of patients, a review of the safety data for this dosage form seemed timely and appropriate. Nondeformable, extended-release tablets and capsules, including those that incorporate OROS® technology, are available and accepted worldwide. The advantages offered by these products are well known: they can provide patterned delivery to meet specific medical needs, minimise fluctuations in drug concentration, extend the duration of action of drugs with short half-lives, and may enhance patient compliance by reducing the number of doses taken each day.[1-4] Disadvantages include the inability to halt drug release during the administration period.

The OROS® osmotic (OSM) dosage form reviewed in this paper optimises extended-release oral administration by controlling the rate of drug release for a predetermined period, providing constant (zero-order release), patterned, or pulsed delivery profiles (figures 1 and 2). The tablet core is surrounded by a membrane that is permeable to water, but impermeable to ions and to the drug itself.[2,3] In the GI tract, the osmotic activity of the core components establishes an osmotic gradient, drawing water into the tablet at a rate controlled by the composition and thickness of the membrane. Drug delivery begins when water enters the tablet to dissolve or suspend the drug in the core; the resulting drug solution or suspension flows out of

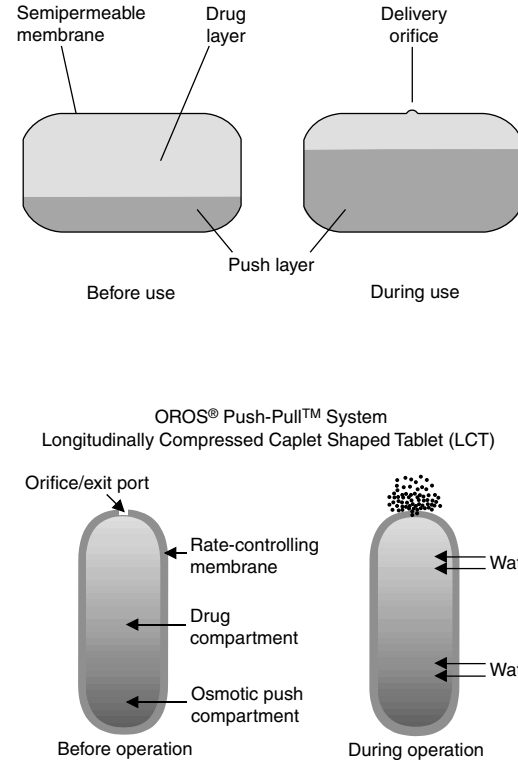

Fig. 1. The core of OROS® osmotic drug delivery technology: cross-sections of bilayer and trilayer tablets before and during use.

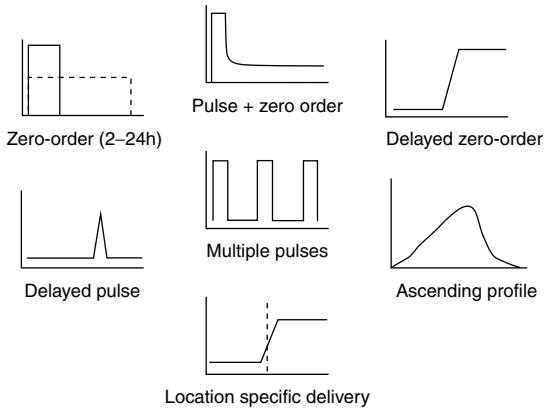

Fig. 2. Examples of OROS® osmotic drug delivery technology delivery profiles.

delivery ports in the membrane at the same rate as the water entering the tablet. Delivery is thus controlled primarily by the dosage form rather than environmental factors such as pH or motility.

Methods

This review focused primarily on publicly available data on the GI safety of OSM products in the US. The safety data analysed in this study were obtained from the published English-language literature and from US FDA postmarketing safety databases available through the Freedom of Information Act (FOIA), supplemented by information from ALZA Corporation's commercial safety database on those OSM products for which ALZA has reporting responsibility.

Scope of the Evaluation

OSM products include prescription medications for urology, CNS, and cardiovascular indications, as well as over-the-counter (OTC) nasal/sinus congestion medications. Seven prescription and one OTC product incorporating OSM technology were available on the US market at the time of writing (figure 3; table I), and were evaluated in this study. Distribution data for the seven prescription products were also obtained, allowing a simple frequency measure for unique reports of GI events involving clinically significant irritation or obstruction to be calculated. Distribution data were not available for the OTC product.

Two products withdrawn from the market for safety reasons were excluded from this analysis: one was never marketed in the US (Osmosin® [indomethacin]), and the other (Acutrim®) was a non-new drug application (non-NDA) product formerly marketed in the US and part of a voluntary withdrawal of all phenylpropanolamine products. No FOIA postmarketing, commercial safety, or distribution data comparable to those for products currently on the market were available to allow the inclusion of these products in this evaluation. Nevertheless, relevant safety issues from the literature are noted in the discussion section. Products approved but not marketed for economic reasons were also excluded from this evaluation (see note in table I).

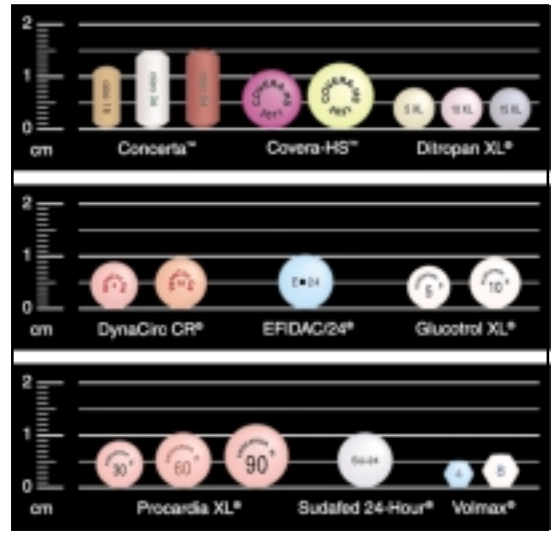

Fig. 3. OROS® osmotic drug delivery technology products: physical characteristics. Seven prescription and one over-the-counter products were studied: Concerta® (methylphenidate HCl); Covera-HS® (verapamil HCl); Ditropan XL® (oxybutynin chloride); DynaCirc CR® (isradipine HCl); Efidac/24® (pseudoephedrine HCl); Glucotrol XL® (glipizide); Procardia XL® (nifedipine); Sudafed® 24-hour (pseudoephedrine HCl); Volmax® (salbutamol [albuterol] sulphate).

Table I. US marketing history of OROS® osmotic drug delivery technology products

Product[a]	US market introduction	Indication
Concerta® (methylphenidate HCl)	2000	Attention deficit hyperactivity disorder symptoms (age ≥6y)
Covera-HS® (verapamil HCl)	1996	Angina and hypertension (adults)
Ditropan XL® (oxybutynin chloride)	1999	Overactive bladder symptoms (adults)
DynaCirc CR® (isradipine HCl)	1997	Hypertension (adults)
Efidac/24® and Sudafed® 24-Hour (pseudoephedrine HCl)	1993	Nasal/sinus congestion (OTC)
Glucotrol XL® (glipizide)	1994	Hyperglycaemia (adults)
Procardia XL® (nifedipine)	1989	Angina and hypertension (adults)
Volmax® (salbutamol [albuterol] sulphate)	1993	Asthma (age ≥6y)

a Does not include Efidac® (brompheniramine maleate/pseudoephedrine HCl), Minipress XL®, Efidac/24® (chlorpheniramine maleate), or Acusystem® C vitamin supplement, all approved in US but not currently marketed for economic reasons; and Acutrim®, launched in 1983 and withdrawn as part of a voluntary withdrawal of phenylpropanolamine products.

OTC = over the counter.

Sources and Scope of Data

Adverse Event Databases

FOIA data were searched for postmarketing reports of GI adverse events for the OSM products currently marketed in the US from January 1, 1983 to June 1, 2000 (table I). The FDA databases, which include reports submitted by both physicians and manufacturers, were the Spontaneous Reporting System (SRS), with historical adverse event data from 1969 through October 1997, and the Adverse Event Reporting System (AERS), with adverse event data collected from November 1997 to the present. Both databases were searched using the ADR Report Builder and dsAnalysis online (Galt Associates, Inc). GI event search terms are listed in table II. All events were included in the total number of events except those in reports that specifically identified non-OROS® products by trade name, dosage strength, descriptor (i.e. immediate-release), NDA number, manufacturer name, or other information.

In addition, commercial safety information was obtained directly from ALZA Corporation's in-house safety database on those OSM products for which ALZA had a reporting responsibility, including two prescription products (Ditropan XL® [oxybutynin chloride] and Concerta® [methylphenidate HCl]) and one non-prescription product marketed under two trade names (Efidac/24® and Sudafed® 24-Hour [pseudoephedrine HCl]).

Duplicate or repeat reports for the same patient/event were identified and confirmed through a review of the original MedWatch or FDA 1 639 reports and by matching event details provided in the FOIA listing. The resulting list of adverse events was then consolidated into a list of unique cases by combining all symptoms reported for each multi-symptom case.

Literature Databases

Using the same search terms as were used to search the adverse event databases (table II), searches were conducted for citations, abstracts, or full-text publications in the English-language literature from 1982 until June 1, 2000 on all OROS® products available on the US market. A similar screening process was used in the literature as with FOIA data: all events were included except those specifically identified by descriptor, manufacturer name, trade name, dosage strength, year of event (e.g. events occurring before OROS® product was available), or other information as referring to non-OROS® products. All searches were conducted in the Dialog® Corporation major biomedical databases (Medline, Embase, Biosis, Scisearch, and Derwent Drug File). In addition, three literature searches were conducted for tablet injury in humans,

Table II. Search terms used to identify Freedom of Information Act postmarketing reports and literature reports of gastrointestinal adverse events with OROS® osmotic drug delivery technology dosage forms (January 1, 1983–June 1, 2000)

Bezoar
Colitis ulcerative
Colonic stenosis
Duodenal ulcer
Duodenal ulcer haemorrhage
Oesophageal stenosis
Oesophageal ulcer
Faecal impaction
Gastric ulcer
Gastric ulcer haemorrhage
Gastric ulcer perforation
Gastrointestinal obstruction NOS
Gastrointestinal ulcer NOS
Ileus
Ileal stenosis
Impaired gastric emptying
Intestinal obstruction
Intestinal stenosis
Intestinal ulcer
Large intestinal ulcer
Peptic ulcer
Peptic ulcer haemorrhage
Pyloric stenosis
Small intestinal obstruction NOS
Ulcer haemorrhage NOS
Volvulus of bowel

NOS = not otherwise specified.

independent of the drug used, to complement the drug-specific search. The first was a free text search in the files named. Terms for gastrointestinal injury were combined with 'oral dosage form' and 'adverse effects' terms appearing anywhere in the records. These results were combined with articles containing any of an extensive list of oral dosage form terms appearing in the title. Two additional searches were conducted in Medline and Embase only, making use of the indexing for GI injury 'aetiology' or 'side effect' and oral dosage form 'adverse effects' or 'foreign bodies' and 'aetiology' available in these databases.

Distribution Data and Estimated Frequency of Unique Reports

Estimated cumulative distribution totals were combined with safety data to determine a simple frequency measure for unique reports of GI events involving clinically significant irritation or obstruction. Distribution data for six of the seven prescription OSM products were derived from IMS National Prescription Audit™ Plus data available in the US from 1995 through 1999, and for Concerta® from launch in August 2000 through to December 2000 (table I). For products launched before 1995 – Glucotrol XL® (glipizide), Procardia XL® (nifedipine), and Volmax® (salbutamol [albuterol]) – cumulative distribution data were estimated by back projection from time of launch to 1995, using a per year average derived from the IMS data. Distribution data were not available for the OTC product.

Results

Overall Rate of Clinically Significant Gastrointestinal (GI) Events

The estimated cumulative distribution of these products in the US through June 2000 is 12.85 billion tablets. A search of the FOIA data and a review of more than 300 articles and abstracts through June 2000 yielded 168 unique cases of clinically significant GI irritation or obstruction associated with OSM products in the US (154 from FOIA, 14 from the literature; table III). Using these figures, the reported incidence of clinically significant GI irritation and obstruction in the US is an estimated 13 cases per billion tablets distributed, or one case per 76 million tablets. The majority (78%) of these cases were reported in patients taking Procardia XL® (approximately one case in 29 million tablets).

Oesophageal Irritation, Injury, and Obstruction

OSM products were associated with a total of four postmarketing reports of oesophageal ulcer and 11 reports of oesophageal obstruction. For reports in which age was specified, the mean age was

69.5 ± 15.5 years, with approximately 80% of these events occurring in patients age 65 or older. Procardia XL® was associated with eight of the 11 reports of obstruction. The other three were associated with Covera-HS® (verapamil HCl), Dynacirc® (isradipine HCl), and Volmax®, respectively. GI histories were available for six of the 11 obstruction reports; three had known strictures, and one each had scleroderma and oesophageal cancer. There were no deaths; one case was considered life-threatening.

Two literature reports of oesophageal obstruction with Procardia XL® also describe pre-existing oesophageal abnormalities: stricture[5] and carcinoma.[6]

Gastric and Lower GI Irritation, Injury, and Obstruction

Irritation and Injury

A total of 59 cases of clinically significant GI irritation and injury were reported in association

Table III. Summary of significant gastrointestinal (GI) adverse event reports and tablet distribution totals for OROS® osmotic drug delivery technology products[a] (postmarketing data obtained from January 1, 1983–June 1, 2000; adjusted for duplication)

Product [US launch year]	Gastric and lower GI obstruction		Other GI effects		Subtotals (no. of unique cases)		Totals	Tablet distribution 1995–1999[b] (estimated cumulative[c])
	FOIA[d]	Lit[e]	FOIA[f]	Lit[g]	FOIA	Lit		
Concerta® (methylphenidate HCl) [2000]	0	1	0	0	0	1	1	22 million
Covera HS® (verapamil HCl) [1996]	5	1	1	1	6	2 (1)[h]	8 (7)[h]	218 million
Ditropan XL® (oxybutynin chloride) [1999]	0	0	0	0	0	0	0	84 million
DynaCirc CR® (isradipine HCl) [1997]	5	0	7	0	12	0	12	21 million
Efidac/24®, Sudafed® 24-Hour (pseudoephedrine HCl) [1993]	5	0	0	1	5	1	6	Data not available
Glucotrol XL® (glipizide) [1994]	5	0	6	0	11	0	11	2.15 billion (2.58 billion)
Procardia XL® (nifedipine) [1989]	85	10	66	6	151	16	167	4.4 billion (9.68 billion)
Volmax® (salbutamol [albuterol] sulphate) [1993]	1	0	2	0	3	0	3	176 million (246.4 million)
Total no. events (unique cases)	106 (82)	12	82 (72)	8	188 (154)[h,i]	20 (14)[h,j]	208 (168)[h]	
Total distribution 1995–1999 (total cumulative[j]) 7.07 billion (12.85 billion)								
Total no. cases/ cumulative distribution 1 case/76 million tablets or 13 cases/billion tablets								

a Data sources: see Methods section.

b Calculated using data from IMS Health, National Prescription Audit™ Plus for January 1, 1995 until December 1999. Ditropan XL® distribution includes samples to physicians. Concerta® data from August 2000 through December 2000.

c Estimated cumulative distribution: back calculated to product launch for products launched before 1995.

d Includes bezoar, colonic stenosis, faecal impaction, gastrointestinal obstruction NOS, ileal stenosis, ileus, ileus paralytic, impaired gastric emptying, intestinal obstruction, intestinal stenosis, pyloric stenosis, volvulus of bowel.

e Includes bezoar, faecal impaction, gastric concretion, gastric outlet obstruction, intestinal obstruction, pyloric stenosis, and small bowel obstruction.

f Includes colitis ulcerative, gastric ulcer, gastric ulcer haemorrhage, gastric ulcer perforation, gastrointestinal ulcer NOS, duodenal ulcer, duodenal ulcer haemorrhage, ileal ulcer, intestinal ulcer, large intestinal ulcer, oesophageal stenosis, oesophageal ulcer, peptic ulcer, peptic ulcer haemorrhage, ulcer haemorrhage NOS.

g Includes bowel ischaemia, duodenal ulcer, intestinal infarction, ischaemic colitis, and oesophageal obstruction.

h Number of unique cases; multisymptom cases were consolidated.

i Total includes 14 cases of oesophageal obstruction (stenosis) and/or oesophageal ulcer.

j Total includes two cases of oesophageal obstruction.

FOIA = Freedom of Information Act reports; **Lit** = published literature reports; **NOS** = not otherwise specified.

with OSM products, including duodenal, gastric, intestinal, ileal, and peptic ulcers with or without haemorrhage (49 cases); small intestinal perforation (two cases); and ulcerative colitis (eight cases) [data from FOIA]. Of the 59 cases, 49 (83%) were associated with Procardia XL®. The average age of patients experiencing GI adverse events in this category was 67.6 ± 14.7 years. One additional case in the literature reported ischaemic colitis in a 58-year-old woman with a history of segmental colitis, who was taking Efidac/24®.[7]

Six deaths were reported in this category (10.1%), including four associated with Procardia XL®: duodenal ulcer haemorrhage (two cases), peptic ulcer haemorrhage (one case), and gastric ulcer (one case). In the two other cases (gastric ulcer haemorrhage associated with isradipine, and peptic ulcer haemorrhage associated with glipizide), it is unclear whether the reports concern the immediate-release or the OSM formulation of the drug, and no information was obtained regarding the patients' GI history. Four other cases were considered life-threatening.

In seven ulcer cases associated with Procardia XL®, pre-existing ulcers and inflamed tissue in the lumen reportedly predisposed patients to tablet retention at or near those sites; in some instances bezoars and/or an intestinal obstruction resulted. In three other cases, the adherence of a tablet to the mucosal wall or the presence of a bezoar of tablets reportedly provided mechanical irritation leading to development of an ulcer or inflamed tissue. One author stated that it was unclear whether the duodenal ulcer and stricture had preceded, or were a consequence of, the bezoar.[8]

Obstruction

OSM products were associated with 82 cases (106 events) that involved one or more symptoms of gastric or lower GI obstruction (data from FOIA and ALZA safety databases). Of these, 57 cases involved only one reported symptom: intestinal obstruction (30 cases), bezoar (11 cases), ileus (six cases), faecal impaction (four cases), stenosis (intestinal or pyloric; three cases), impaired gastric emptying (two cases), or volvulus of the bowel (one case). The remaining 25 cases were reported to involve at least one symptom of intestinal obstruction in combination with one or more other clinically significant GI symptoms. Fifteen (60%) of the 25 multisymptom cases involved both an obstruction and a bezoar. Procardia XL® was associated with 78% of obstruction cases.

Three deaths were reported in this category (3.6%); three other cases were considered life-threatening. Two of the deaths were in an 86-year-old man and a 76-year-old woman, both with pre-existing GI anatomic defects, who were taking Procardia XL®; one of the patients had extensive previous surgery including gastro-jejunostomy. The third death, resulting from pulmonary thromboembolus, infectious chronic obstructive pulmonary disease, and paralytic ileus, was in a 67-year-old man who had been taking Volmax®.

The literature search found 14 published reports of lower GI obstruction, 13 in association with Procardia XL® (table IV), and one with Covera-HS®. Four of these reports were identified as events included in the FOIA databases. The remaining ten unique cases included small bowel/intestinal obstruction (two cases, one resulting in death), bezoar (six cases), and gastric concretion with intestinal infarction (two cases, both resulting in death). The two fatal cases of gastric concretion were in patients who had intentionally taken overdoses of Procardia XL® and Covera-HS®, respectively, in apparent suicides.[9,10] The third death was associated with Procardia XL® use in an 88-year-old woman; the authors noted the likely contribution not only of the retained tablets but also of underlying disease (especially colonic ischaemia) to the patient's GI symptoms.[11] In patients with gastroplasty, obstruction occurred when patients were switched from a 30 or 60mg tablet to the 90mg tablet.[12]

Patient GI histories were available for 33 (40%) of the 82 FOIA cases and for the ten unique published reports of obstruction. Of these 43 case histories, ten patients had stricture, stated narrowing of the GI tract, or GI malignancy, and 13 patients

Table IV. Published reports of lower gastrointestinal (GI) obstruction associated with Procardia XL® (nifedipine): patient information

Event	Patient history, concurrent conditions	Gender/age (y)	Reference
Gastric obstruction	Gastroplasty 3 years before	F/48	13[a]
Gastric outlet obstruction	Gastroplasty 5 years before	F/33	12[a]
Small bowel obstruction	Prior abdominal surgeries; partial small bowel obstruction; adhesions	F/78	14
Bezoar, gastric; duodenal ulcer	Peptic ulcer disease, stricture	M/59	8
Bezoar, gastric	Billroth II procedure 30 years prior; stricture at anastomotic orifice 3 years prior	M/65	15
Bezoar	Volvulus in sigmoid colon	Not known	16
Bezoar, colon; faecal impaction	Rectosigmoid stricture	M/79	17[a]
Gastric concretion; intestinal infarction	Voluntary drug overdose; no history of GI tract abnormality	M/37	10
Bezoar, colon	3 prior abdominal surgeries, including temporary colostomy; reanostomosis; decreased intestinal motility	M/69	18
Bezoar, small bowel	Prior nephrectomy; chronic small bowel obstruction	M/70	19
Ischaemic colitis; intestinal obstruction	Serious coexisting disease	F/88	11
Bezoar; small bowel obstruction	GORD; concurrent tumour mass in small intestine	M/76	20[a]
Bezoar; duodenal ulcer	GORD; peptic ulcer disease	F/77	21

a US FDA Freedom of Information Act report for this event.

F = female; **GORD** = gastro-oesophageal reflux disease; **M** = male.

had previous intestinal surgery (e.g. resection, gastroplasty), with subsequent adhesions noted in three patients, and/or a history of small bowel obstruction. Another 14 patients had a medical history of other GI conditions potentially predisposing to narrowing or slowed motility, including diverticulitis, Crohn's disease, chronic constipation, and ileus.

Safety of OROS® Products in Special Populations

Elderly Patients

Two published comparative clinical studies evaluating the effect of age on the safety of Ditropan XL® and Glucotrol XL® formulations found that adverse events did not increase with age. In patients with urge urinary incontinence or mixed incontinence with a significant urge component, the incidences of adverse events with Ditropan XL® and immediate-release oxybutynin were reported to be comparable for patients aged >65 years and those aged <65 years.[22] Similarly, in a placebo-controlled study with 594 patients with type 2 diabetes mellitus, the efficacy and safety of Glucotrol XL® were reportedly not affected by patient age.[23]

The average age of patients reporting clinically significant GI irritation or injury in association with OSM products was 68.0 ± 14.8 years. Information is available for 70 of the 82 cases of gastric or lower GI obstruction: the average age of patients reporting a GI obstruction was 64.1 ± 15.7 years (n = 70). The average age of the total patient population using OSM products is not known.

Paediatric Patients

The two OSM products (Volmax® and Concerta®) prescribed to patients ≥6 years in the US have a combined distribution of 37.7 million doses, with one oesophageal obstruction reported in a 16-year-old patient. The tablet required removal by esophagoscopy.[24]

In clinical trial literature, Concerta® was well tolerated in children aged 6–13 years with attention

deficit hyperactivity disorder (ADHD).[25-29] GI events with Concerta® were similar to those with immediate-release methylphenidate in studies with a total of 1 552 patients aged ≤18 years.[25,26,29]

Discussion

OROS® Osmotic Products Withdrawn from the Market

Two OSM products withdrawn from the market for safety reasons were not included in this review.

In 2000, a non-NDA appetite suppressant (Acutrim®) was withdrawn from the US market as part of the voluntary withdrawal of all products containing phenylpropanolamine.[30,31]

In 1983, an indomethacin product using the OSM drug delivery technology (Osmosin®) was withdrawn from the UK market after literature reports of intestinal ulcer, perforation, and death in elderly patients.[32-40] The product had been introduced in European countries under the trademarks Osmosin® or Osmogits® (indomethacin 85mg as the sodium salt). The approximately 400 000 prescriptions written in the first 6 months for Osmosin® were associated with some 200 (0.05%) yellow card reports to the UK Medicines Control Agency on suspected adverse reactions, including reports of intestinal perforation and death (36 reports), primarily in elderly patients.[32,41] The UK Committee on Safety of Medicines issued a cautionary statement, and worldwide sales were suspended.[42] Although pharmaceutical, animal, and human safety studies did not show that Osmosin® produced more serious GI adverse reactions than other nonsteroidal anti-inflammatory drugs (NSAIDs), the product was not reintroduced and the pending US NDA was withdrawn.[42] Osmosin® was one of four NSAIDs removed from the UK market in a 2-year period.[34]

There is some evidence that the product was preferentially prescribed to elderly patients unable to tolerate immediate-release indomethacin, often at higher than recommended doses[43-45] and in some cases in conjunction with other NSAIDs.

Premarket and subsequent clinical studies, which excluded patients who could not tolerate immediate-release indomethacin, reported no more, and in some cases fewer, adverse events with the OSM formulation than with immediate-release indomethacin.[46-49]

GI irritation with NSAIDs is extensively documented.[32,41,50-57] Ulceration, stricture, and perforation of the lower intestine and bowel were reported as early as 1966 with immediate-release indomethacin.[58-60] Such effects were also described in association with the NSAID diclofenac in immediate-, delayed-, and extended-release formulations.[61-65] Reports of such injury with NSAIDs have increased in frequency over the past few decades.[61,66-73] Bjarnason and colleagues[38] noted that effects of NSAIDs on the large intestine are rare, but involve significant symptoms and some morbidity; effects on the small intestine, including those reported with Osmosin®, include ulcerations and perforations. Such injury is reportedly due in part to the inhibition by NSAIDs of prostaglandin generation.[38]

Irritation and Injury

GI injury is a known effect of oral medication, and has been reported with more than 100 drugs in both immediate- and extended-release formulations.[74-77] A review of pill-induced oesophagitis notes that, over a 30-year period, the world literature cites 979 cases of oesophageal injury and obstruction; nearly half of these cases implicated approximately 30 different antibacterials (primarily doxycycline and tetracyclines[78-80]) and antivirals.[76]

Some authors speculate that sustained-release dosage forms designed to release drug in the lower intestine have shifted the site of irritation to the lower intestine,[63,68,81] although one study suggests the importance of this change is overestimated.[82] Others note that the increasing use of new diagnostic methods allows the diagnosis of elusive and sometimes asymptomatic conditions.[67,83] Physicians prescribing an extended-release product

delivering a drug known to be irritating should exercise the same caution and attention to a patient history of intolerance that they would for immediate-release formulations.

Obstruction

Oesophageal and lower GI obstruction are also known effects of oral medication, often in patients with a history of structural abnormality or motility disorder.[13,77,84-91] Even in the case of a guar gum-containing diet product (Cal-Ban 3000®) that swelled to 10- to 20-fold its initial size, pre-existing oesophageal or gastric disorders were present in approximately 50% of the 26 oesophageal and small bowel obstructions reported.[92,93]

The association of obstruction reports with pre-existing GI narrowing led to the revision of the Procardia XL® product label in 1990 to include the following cautionary text: 'as with any other non-deformable material, caution should be used when administering Procardia XL® in patients with pre-existing severe gastrointestinal narrowing (pathogenic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of Procardia XL®'. Similar text appears in the labels of all OSM products.

A similar label revision occurred in 1997 for a non-OSM extended-release dosage form delivering loratadine and pseudoephedrine sulfate (Claritin-D® 24-hour tablets). In its first year on the market, the product was associated with 24 reports of oesophageal obstruction, an incidence of one report per 100 000 prescriptions.[94,95] The label was revised to state that patients with a history of difficulty in swallowing tablets or known upper GI narrowing or abnormal peristalsis should not use the product,[96] and the tablets were reformulated in 1998 to a new oval shape. A history of pre-existing GI disorders or abnormalities was a factor in approximately half the incidents.[94,95] The effect of the reformulation on the incidence of obstruction is not known. Physicians can lessen the incidence of oesophageal retention by stressing the importance of adequate fluids and an upright posture while taking oral medication.[84,97,98]

Pharmacobezoars occur rarely but with a broad range of products.[20] Risk factors identified in reports of bezoars include alterations in GI anatomy and dysmotility.[20,99,100] Physicians should also be alert to the presence of concomitant medications, such as those used to treat cystic fibrosis (e.g. ipratropium bromide), that are frequently associated with bezoar formation.[20]

Limitations of the Study

This study focused primarily on publicly available data on adverse events that were reported in the US and the English-language literature. As OSM products are increasingly introduced in international markets, study of their worldwide safety profile would be of benefit. The US adverse event databases used in this study rely on spontaneous reporting from patients and healthcare providers, and may reflect only a portion of the true incidence of events. In addition, new products and new technologies tend to generate greater attention and more conscientious reporting in the early years following their introduction.

Conclusions

The safety and effectiveness of various OSM products were reviewed.[101-105] Reports of adverse events from clinical trials with OSM products tend to be consistent with known effects of the same drug substances in other formulations.[25,26,29,101,106-108] Although some reports suggest that extended-release products pose a greater risk of injury and obstruction than other oral dosage forms, a review of long-term safety experience with products using OSM controlled-release technology yields a low incidence of clinically significant GI irritation and obstruction: approximately one case in more than 76 million tablets distributed. Oesophageal and lower GI irritation and injury reported with OSM products were infrequent and, for lower GI irritation particularly, typically associated with known effects of the drug sub-

stance rather than the dosage form. The incidence with Procardia XL® (approximately one case in 29 million tablets) is low given the elderly population and disease state the drug is used to treat.

Elderly patients represent a substantial portion of the OSM patient population, and their experience is reflected in the overall low frequency of events. With the introduction of Concerta® for ADHD, the paediatric population receiving OSM products has grown considerably; however, incidence rates remain low.

Physicians can minimise GI injury and obstruction with tablets and capsules by providing clear messages about proper administration, including reminders to take medication with liberal fluids and in an upright position, and by close attention to patient history of intolerance or GI narrowing. Nondeformable tablets such as OSM products also carry label instructions not to chew, crush, or divide tablets. Properly prescribed, extended-release products provide substantial therapeutic and convenience benefits without additional risk.

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