The Influence of Polyethylene Glycol Solution on the Dissolution Rate of Sustained Release Morphine

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Abstract

Introduction Whole bowel irrigation (WBI) is a management option for overdose of medications poorly adsorbed to activated charcoal, with modified release properties, or for body packers. Polyethylene glycol (PEG) is a mixture of ethylene oxide polymers of varying molecular weight. PEG with an average molecular weight of 3350 g/mol is used for WBI. PEG electrolyte lavage solution has been shown in vitro to hasten the dissolution of acetaminophen. The impact of PEG on the pharmacokinetics of extended release pharmaceuticals is unknown. Lower average molecular weight PEG mixtures are used as solvents and excipients. We sought to investigate the impact of PEG on the release of morphine from several extended release morphine formulations.

Methods An in vitro gastric model was developed. To test the validity of our model, we first investigated the previously

described interaction of ethanol and Avinza®. Once demonstrated, we then investigated the effect of PEG with several extended release morphine formulations.

Results In the validation portion of our study, we confirmed an ethanol Avinza® interaction. Subsequently, we did not observe accelerated release of morphine from Avinza® or generic extended release morphine in the presence of PEG.

Conclusion The use of PEG for gastric decontamination following ingestion of these extended release morphine formulations is unlikely to accelerate morphine release and aggravate intoxication.

Keywords Gastric decontamination · Whole bowel irrigation · In vitro drug release · Modified release morphine · Delayed release preparations · Morphine/pharmacokinetics

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Introduction

Whole bowel irrigation (WBI) is a management option for potentially severe overdoses of medications that are poorly adsorbed to activated charcoal, such as iron and lithium, following the ingestion of an extended-release (ER) formulation of a medication, or for a body packer [1]. WBI is typically carried out using polyethylene glycol solution (PEG), a mixture of ethylene oxide polymers [H-(OCH₂-CH₂)_n-OH] with an average molecular weight of 3350 g/mol. Other PEG mixtures of lower molecular weight are used as ointment bases and excipients in pharmaceuticals, and also as surfactants, dispersing agents, and solvents [2]. There is a possibility that PEG could likewise act as a solvent, since an in vitro model demonstrated that PEG electrolyte solution hastened the dissolution of standard release acetaminophen [3]. The impact of PEG on the dissolution kinetics of ER pharmaceuticals is unknown.

Opioid intoxication has reached epidemic proportions in the USA [4]. In our experience, individuals ingesting ER opioids may have delayed or recurrent toxicity and our poison center routinely recommends a more prolonged observation period in these instances [5]. Although toxicity can be readily managed with naloxone boluses and/or continuous infusion, the endpoint for discontinuation of antidotal therapy—resolution of opioid effects—while relatively straightforward with short half-life or immediate-release opioids, is more difficult with these ER products. Prolonged or delayed toxicity may be seen. In our experience, naloxone continuous infusions may be needed for prolonged periods of time. Discontinuation too early can result in the tragic recurrence of opioid respiratory depression and death. Gastrointestinal decontamination with WBI is another consideration if there are no contraindications, since clearing the gut of ER products would theoretically shorten the duration of naloxone requirements, possibly reduce length of stay, and potentially avoid recurrence of respiratory depression. The clinical question we sought to address is whether PEG results in dose-dumping, the premature release of morphine from ER formulations. If this were the case, it is possible that a patient could experience accelerated release of morphine during WBI and be at risk of increased opioid toxicity from the GI decontamination procedure.

There is reason for concern regarding rapid dissolution of ER opioids, since it has been demonstrated that ethanol can accelerate the release of opioid from several ER opioid formulations. Palladone®, an ER hydromorphone product, was withdrawn from the US market by its manufacturer Purdue Pharma in July 2005 after the United States Food and Drug Administration (FDA) issued a warning regarding the premature release of hydromorphone from Palladone® when co-ingested with ethanol [6]. Similarly, Avinza®, another ER morphine formulation, received a black box warning later that same year when a similar effect was observed *in vitro* with ethanol [7]. Specifically, the FDA Dear Doctor letter stated that patients must not consume alcoholic beverages while using Avinza® and additionally that patients must not use other medications, prescription or otherwise, that contain alcohol. The warning stated that consumption of ethanol while taking Avinza® could result in the rapid release of a fatal dose of morphine. A search of the peer-reviewed literature and the FDA website failed to reveal the experimental protocol and procedure used to demonstrate this effect between Avinza® and ethanol (Ovid and Medline searches performed Jan. 2010, at the time this study was considered).

Our goal was to assess the impact of PEG 3350 solution on several ER morphine products. We first devised a simple *in vitro* model utilizing readily available equipment and reagents and sought to confirm that this model could reproduce the

FDA's findings of more-rapid dissolution of Avinza® by ethanol. If we were able to demonstrate this interaction, we would proceed with testing several ER morphine products and PEG 3350 solution using the same model.

Methods

All tests were performed in a large agitated water bath apparatus heated to 37 °C. Simulated gastric fluid was prepared per US Pharmacopeia Volume XXIII [8]. Two grams (g) of NaCl and 3.2 g of purified pepsin, derived from porcine stomach mucosa (Sigma-Aldrich, St. Louis, MO), were added to 7.0 mL of 0.1 N HCl and water to a final volume of 1 L. The pH of the simulated gastric fluid was 2.4 (average of 5 measurements). Forty (40 %) and eighty percent (80 %) ethanol solutions were prepared from stock 95 % ethanol. PEG solution was prepared by adding 35.5 g of Miralax® to 500 mL water. The pH of this solution was 8.0 (average of five measurements). (For comparison to other PEG solutions, GoLytely® contains 29.5 g PEG/500 mL solution and NuLytely® and HalfLytely® both have 52.5 g/500 mL solution [9, 10]).

One hundred milliliter of simulated gastric fluid were mixed with (a) 100 mL of water, (b) 100 mL of 40 % ethanol for a final ethanol concentration of 20 %, or (c) 100 mL of 80 % ethanol for a final ethanol concentration of 40 % and placed in 250-mL Erlenmeyer flasks. The solutions were placed in an agitated water bath at 37 °C for 30 min. At that time, one intact 90-mg Avinza® capsule was added to each flask. One-milliliter samples were removed at 30, 60, and 90 min (without fluid replacement). Specimens were split and frozen at –70 °C until analysis.

For comparison of ethanol with water, sample size was calculated using G*Power 3.10 (Universität Kiel, Germany). For a medium effect size of 0.50 with an alpha error of 0.05 and a power of 0.80, a total sample size of 30 was needed, 10 per group.

For the second part of this study, simulated gastric solution was prepared as above. Aliquots of 100 mL of simulated gastric fluid were warmed to 37 °C in an agitated water bath, and a study drug was added. After 30 min, 100 mL of either PEG solution or 100 mL of water was added. The pH of the final solution, simulated gastric fluid with PEG, was 2.6 (average of five measurements). One-milliliter samples were withdrawn at 30, 60, and 90 min after the addition of PEG solution or water. Samples were split and frozen at –70 °C until analysis.

To compare PEG to water, we estimated a sample size using an effect size of 0.5, an alpha error of 0.05 and power of 0.80. This calculation resulted in a sample size of 22 for each drug tested, 11 with PEG solution and 11 with water. We tested Avinza® 90-mg capsules, Kadian® 100-mg capsules,

and a generic ER morphine 100-mg tablet (Mallinckrodt Pharmaceuticals, Dublin, Ireland).

Sample Analysis

Manual extraction of morphine from gastric fluid solutions was performed with a copolymeric bonded phase for drug testing CLEAN SCREEN® DAU Extraction Column (United Chemical Technologies UCT, Inc., Bristol, PA) following a procedure developed by the manufacturer [11]. Briefly, a solution of 200 μ L of gastric fluid, 10 μ L of a 1 mg/mL morphine-d3 solution as internal standard, and buffered with 3 mL phosphate buffer pH 6 was loaded on the DAU sorbent. After washing, the analytes were eluted in an elution buffer prepared from methylene chloride, isopropanol, and ammonia. The eluate was dried in a stream of nitrogen, and the analytes were derivatized at 70 °C in a mixture of 50 μ L BSTFA/TMCS (33148 Supelco, Sigma-Aldrich St. Louis, MO) and 50 μ L ethyl acetate. After further dilution to 400 μ L, quantification was performed on a Shimadzu QC2010Plus gas chromatograph with an AOC-5000 autosampler with liquid injection combined with a TQ8030 mass spectrometer (TU Graz, Austria) in multiple reaction mode (MRM), reference ion 429.30 > 236.20 and 432.30 > 239.20, daughter ions, 220.10 > 205.10 and 223.10 > 205.10 for morphine and morphine-d3, respectively. Collision energies were set to 15 for the transitions 429.30 > 236.20 and 432.30 > 239.20 and to 12 for the transitions 220.10 > 205.10 and 223.10 > 205.10. Electron multiplier voltage was set to 1.3 kV, and the resolution of quadrupole 1 and 3 was set to “high resolution.” The injection port temperature was at 240 °C, oven temperature was held at 150 °C for 1 min following injection and programmed to 290 °C at a rate of 20 °C/min. Helium was used as the carrier gas and the flow rate was set at 1.1 mL/min in the constant flow mode.

Fig. 1 Avinza® capsules in simulated gastric solution with either water (blue line (diamond) +/- CI), 20 % ethanol final concentration (red line (circle) +/- CI) or 40 % ethanol final concentration (lime green line (square) +/- CI)

Results

The initial portion of our study demonstrates the dramatic effect of ethanol on the release of morphine from Avinza®. The concentration of morphine in simulated gastric fluid with water at 30, 60, and 90 min was 35.7 mg/L (CI 34.2–37.1 mg/L), 40.0 mg/dL (36.0–44.0 mg/L), and 50.7 mg/L (46.9–54.4 mg/L) respectively compared to 98.0 mg/L (52.8–143.2 mg/L), 187.6 mg/L (153.1–222.1 mg/L), and 238.3 mg/dL (205.0–271.6 mg/L) for Avinza® in simulated gastric fluid with a final ethanol concentration of 20 %. For 40 % final ethanol concentration, these values were 209.9 mg/L (89.5–330.3 mg/L) at 30 min, 281.3 mg/L (244.0–318.6 mg/L) at 60 min, and 307.3 mg/L (288.9–325.7 mg/L) at 90 min (see Fig. 1). With a final 40 % ethanol solution we observed a greater degree of variability in morphine concentrations at 30 min as well as one clear outlier that precluded any statistical comparison between the 20 and 40 % solutions. These results indicated that our model had validity and would be suitable to progress to part 2 of this study.

Figures 2 and 3 compare the impact of PEG solution compared to water on the release of morphine from Avinza® and generic ER morphine. PEG solution did not demonstrate any impact on the ER properties of either of these two medications. The concentration of Kadian® detected was less than the level of quantification for our calibration curve, 10 mg/L, at all time points measured.

Discussion

Our proof of method, part 1 of this study, affirms the FDA finding of a pharmacokinetic effect from the combination of ethanol with Avinza®, in addition to the recognized dangerous pharmacodynamic effect of this combination [12]. Our findings suggest the use of PEG to achieve WBI in an attempt to reduce absorption of morphine from the ER products we studied does not result in the accelerated release of morphine.

Fig. 2 Avinza® in simulated gastric fluid with water (blue line (diamond) $\pm$ CI) or PEG solution (red line (circle) $\pm$ CI)

Unexpectedly, we were unable to detect any meaningful release of morphine from Kadian® under the conditions of our study. An investigation of the unique formulation of Kadian® reveals distinct properties of the constituents of Kadian® that likely explain our results. Kadian® capsules contain pellets coated with a methacrylic acid copolymer which is resistant to dissolution at acid pH and soluble at the more alkaline pH of the small bowel [13]. We suspect our results reflect this resistance to acid dissolution since our entire procedure was carried out at an acidic pH.

WBI may be a reasonable decontamination strategy when managing a patient with overdose of Avinza® or a generic extended-release morphine product. For this to be considered, the patient would need to be evaluated prior to the development of significant toxicity and ileus. We recommend close

monitoring of any ER opioid overdose, particularly when this intervention is implemented. Clearing the GI tract of these formulations could reduce further absorption and shorten the duration of opioid effects. Close monitoring of all patients with opioid intoxication is mandatory, particularly those with an unprotected airway and/or exhibiting CNS depression.

Limitations

There are several limitations to our study. We were unable to locate either on the FDA web site or in peer-reviewed literature the experimental procedure used by the FDA to demonstrate accelerated release of morphine from Avinza® in the presence of ethanol. Based on the FDA guidance to industry

Fig. 3 Generic extended-release morphine in simulated gastric fluid with water (blue line (diamond) $\pm$ CI) or PEG solution (red line (circle) $\pm$ CI), sampled at 30, 60, and 90 min

regarding in vitro dissolution studies, we suspect our model does not approach the complexity of that used by the FDA [14]. It is possible that had we used a different dissolution model to test our hypothesis our results may have differed.

We also conducted the entire experiment at an acidic pH. This does not reflect the dynamic processes taking place from an acidic gastric milieu to the more neutral to slightly basic duodenal pH. It is possible that at a more alkaline pH the dissolution kinetics of these medications would be different. This is especially true of Kadian®, formulated to resist dissolution until in a more alkaline milieu. Therefore, we caution that conclusions about the safety of PEG use with Kadian® ingestions cannot be inferred from this data. Our PEG 3350 solution was also devoid of electrolytes. GoLytely®, HalfLytely®, and NuLytely® all also contain several salts. We cannot exclude the possibility that this may also have impacted our results although we do not believe that this is likely. Ideally, we would have performed this study using both PEG solution with and without electrolytes.

We looked at the impact of ethanol and PEG on morphine release from a single capsule. The release kinetics of a larger burden of pills in a true overdose setting may behave quite differently. However, with respect to PEG solution, we would not expect multiple capsules to result in greater proportional release of morphine than the amount released from a single tablet.

Our procedure also accepted that on each subsequent sampling, our total volume decreased by approximately 0.5 % (a total of 3 mL removed from 200 mL). This small volume change and its impact would be expected to be trivial with respect to the concentrations measured and the variance of measurement on each specimen. Additionally, there was a small evaporative loss over the course of the experiment, especially with the ethanol solutions, again likely trivial with respect to the concentrations measured.

Finally, in vitro findings may not replicate in vivo effects. For example, Opana®, an ER oxymorphone formulation, did not have any significant ethanol interaction in an in vitro study, but in vivo a pharmacokinetic interaction has been demonstrated [15].

Conclusions

The use of WBI using PEG solution is unlikely to accelerate the release of morphine from Avinza® or generic ER morphine. This suggests WBI may be a reasonable consideration when managing a patient with overdose of Avinza® or a generic extended-release morphine product.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts to declare.

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