Dissolution of Common Psychiatric Medications in a Roux-en-Y Gastric Bypass Model

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Large numbers of Roux-en-Y gastric bypass (RYGB) surgery patients have psychiatric illnesses that are in part treated with medication preoperatively, but there are no objective data to guide psychiatric drug dosing postoperatively. An in vitro drug dissolution model was developed to approximate the gastrointestinal environment of the preoperative (control) and post-RYGB states. Medication tablets were placed in the two environments, and the median calculated weights of the dissolved portions were compared. Ten of 22 psychiatric medication preparations had significantly less dissolution and two had significantly greater dissolution in the post-RYGB environment, compared with the control environment. The results suggest a need for an in vivo study of serum drug levels after RYGB surgery in patients taking psychiatric medications. Differences in the pharmacokinetics of the postoperative RYGB patient may necessitate adjustments in dosing.
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Roux-en-Y gastric bypass (RYGB) surgery has emerged as a popular, "last-option," but highly effective method for weight loss in morbidly obese individuals. These patients select the surgical option after having failed to achieve control over their obesity through other exhaustive measures. One of the most commonly described motivations of patients is to seek a decrease in the morbidity and mortality that is often associated with chronic, intervention-resistant obesity.

Patients with morbid obesity often have several other medical problems, and extensive prescreening is warranted to best prepare them for the surgery. Consistent with many centers that offer this surgery, a preoperative psychiatric consultation has been routinely completed at Wilford Hall Medical Center. We found that a large number of patients electing to have this surgery had comorbid psychiatric illnesses, such as depression, anxiety, and posttraumatic stress disorder. Within this subgroup, many were taking psychiatric medications before the surgery. A chart review of the 74 psychiatric consultations done in 2002 at Wilford Hall Medical Center for preoperative RYGB patients noted that 25 (34%) were taking psychiatric medications. The five most common medications were venlafaxine (N = 7), valproic acid (N = 6), citalopram (N = 5), sertraline (N = 5), and fluoxetine (N = 4).

Management of these medications peri- and postoperatively can present unique challenges and currently is guided only by clinical judgment. There is scant literature regarding psychiatric illnesses and this population overall. We were unable to find any published research reports regarding the management of psychiatric medications after RYGB, except for a single case report on haloperidol pharmacokinetics.[1] The clinical practice of the local surgeons has been to recommend crushing all medications, and transitioning any sustained-release formulations to instant-release formulations. Otherwise, psychiatric medication ad-

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justments post-RYGB have been made on a case-by-case basis by the patient's outpatient psychiatrist.

Functionally, the RYGB patient has a unique digestive tract. It begins with a nonacid producing gastric pouch of 30 cm^3, which empties within 60 seconds directly into the upper jejenum.[2] There is almost no pepsin[3] and certainly no active pepsin (at pH >5.0 pepsin is inactive). It is assumed other digestive enzymes such as amylases, lipases, and various proteases should still be secreted in the RYGB patient because of intact enteral reflexes and hormonal (i.e., secretin) activity.[4] Pharmacokinetics are thus likely to be significantly affected by these anatomic and chemical differences.

As a starting point, we chose to investigate variability in drug dissolution. We hypothesized that dissolution of psychiatric medications in a post-RYGB bench-top model is either faster or slower than in a preoperative control model.

METHOD

The dissolution fractions of 22 common psychiatric medications (listed in Table 1) were tested in experimental media. Only instant-release tablet preparations were used. The media and manipulation of the media were designed to approximate the gastrointestinal tract of a post-RYGB patient and of a preoperative comparison patient. Thus, two dissolution environments were used.

Both environments utilized a preheated dissolution medium (lactated ringers at 37°C). The post-RYGB environment had a pH of 6.8 ("intestinal"), and the control environment had a pH of 1.2 ("gastric").[5] Adjustment to reach the proper pH was made by micropipette addition of hydrochloric acid (control model) or sodium bicarbonate (post-RYGB model), as needed. Lactated ringers with a pH of 6.0–7.5 is a poor acid-base buffer and thus was easily adjusted to the required pH.

Electrolyte composition was identical between the models. Each 100 ml contained 600 mg of sodium chloride, 310 mg of sodium lactate, 30 mg of potassium chloride, and 20 mg of calcium chloride. Milliequivalents per liter were 130 meq/liter for sodium, 4 meq/liter for potassium, 2.7 meq/liter for calcium, 109 meq/liter for chloride, and 28 meq/liter for lactate. Osmolarity was 273 mOsmol/liter. Thirty milliliters of medium were utilized in 50-ml test tubes for each environment. This approach approximated the 30-cm^3 size of the post-RYGB gastric pouch and thus the upper limit of a jejunum chyme bolus in the RYGB patient. Simulation of bile and pancreatic secretions into the gut was not done because of the added complexity of including these features, but bicarbonate was used to increase the pH of the lactated ringers. Pepsin, which is present in a normal stomach but not in the post-RYGB gastric pouch, is not believed to affect drug dissolution.[6]

In the control model, noncrushed tablets were individually added to the "gastric" medium for 60 minutes, and the test tubes were placed on an orbital shaker (37°C) at 100 rpm for the first 5 minutes, then at 50 rpm thereafter to simulate gastric motility. After 1 hour, the media-pill mixture was centrifuged at 3000 rpm for 15 minutes. The liquid fraction was carefully removed by vacuum pipette aspiration. Thirty milliliters of the neutral "intestinal" solution was then added to the tube with the residual tablet material, and the pH was adjusted if needed to 6.8 by addition of bicarbonate. The new mixture was exposed for 60 minutes on the heated orbital shaker (50 rpm).

After this second hour, the sample was again centrifuged for 15 minutes at 3000 rpm, and the liquid fraction was removed by diligent vacuum aspiration. Any remaining liquid was evaporated by placing the tubes back inside the heated orbital shaker until no visible liquid remained. At no time did the temperature of the heating process exceed 70°C, as the lowest melting point of any of the study medications was that of trazodone at 86°C.[7] The pellet and test tube were digitally weighed, and the weight was subtracted from the original weight of the test tube plus tablet to calculate the amount of the dissolved tablet.

For the post-RYGB model, medications were crushed with a mortar and pestle, as this preparation is used clinically with the RYGB population. The procedure was identical to that for the control model, except the crushed tablet was added to the RYGB medium (pH 6.8) for 2 hours and spun on the centrifuge once at the end of 2 hours. Thus the first 2 hours of gastrointestinal exposure was simulated in both the control and the RYGB models.

Three trials were conducted for each medication in each of the two media. A sample size of three pills per environment provided 80% power to detect a very small effect size (effect size = 0.2, about five standard deviations) between models. The sample size did, however, provide 99% power to detect very large differences (10 standard deviations). The alpha level was 0.05. The independent variable was the medium content (pH) and process as defined earlier (RYGB model versus control model). The dependent variable was the calculated quantity of tablet dissolution.

The calculated weights of the dissolved portions were compared between the control and the RYGB models for

each medication. A Student's t test for each drug was initially planned for the comparisons between the two models. On first analysis, however, the parametric quality of the data could not be confirmed. For this reason, a nonparametric test was selected (Mann-Whitney U), and medians rather than means are reported. Two-tailed significance levels were chosen, as dissolution differences were expected to vary in direction within the models.

RESULTS

Twelve of the 22 medication preparations were found to dissolve differently across the two environments. Ten of the 12 dissolved more in the control model, and only two dissolved to a greater degree in the RYGB model. Although not reported, variability within each sample of three pills was minimal. In no case did a value stray beyond 10% difference from the median weight change. (Variability data are available from the authors.) We chose not to report standard deviations, as we could not confirm that the data were parametric. Reporting the high and low values in addition to the median seemed unhelpful, considering that there were only three pills in each sample.

Within the antidepressant class, bupropion was the only agent that dissolved to a greater degree in the RYGB model (a median of 450 mg dissolved, compared with 320 mg in the control model, $p<0.05$). The dissolution of citalopram and venlafaxine did not differ between conditions. The remaining antidepressant medications (amitriptyline, fluoxetine, paroxetine, sertraline) dissolved more in the control model than in the RYGB model (Table 1).

Among the anxiolytic/sedatives, only one of the six medications varied between the conditions. Clonazepam was found to dissolve slightly more in the control model (a median of 100 mg dissolved, compared with 90 mg in the RYGB model, $p<0.05$). Dissolution of the remaining agents (buspirone, diazepam, lorazepam, trazodone, zolpidem) did not differ between conditions (Table 1).

For the antipsychotic/miscellaneous category, lithium carbonate dissolved significantly more in the RYGB model

TABLE 1. Weights of Dissolved Portions of Psychiatric Medications in Standardized Dissolution Test Models of the Gastrointestinal Environments of Preoperative and Postoperative Roux-en-Y Gastric Bypass (RYGB) Patients

		Preoperative (Control) Environment		Post-RYGB Environment		
Medication	Dose (mg/day)	Median weight of dissolved portion (mg)	%[a]	Median weight of dissolved portion (mg)	%[a]	p[b]
Antidepressants						
Amitriptyline	75	80	28	60	21	<0.04
Fluoxetine	20	110	30	40	11	<0.04
Paroxetine	20	30	09	10	03	<0.04
Sertraline	100	50	16	30	10	<0.04
Bupropion	100	320	52	450	73	<0.05
Venlafaxine	75	180	59	180	59	n.s.
Citalopram	20	70	27	80	31	n.s.
Anxiolytics, sedatives						
Clonazepam	0.5	100	57	90	52	<0.05
Buspirone	10	120	59	120	59	n.s.
Diazepam	5	10	6	10	6	n.s.
Lorazepam	1	10	8	0	0	n.s.
Trazodone	100	330	59	330	59	n.s.
Zolpidem	5	100	82	90	74	n.s.
Antipsychotics/miscellaneous						
Clozapine	100	190	54	150	43	<0.05
Olanzapine	10	190	45	160	38	<0.05
Quetiapine	200	270	53	120	23	<0.05
Risperidone	2	130	64	100	49	<0.05
Ziprasidone	80	280	77	210	27	0.05
Lithium carbonate	300	130	35	280	75	<0.05
Haloperidol	2	10	7	10	7	n.s.
Methylphenidate	20	70	48	80	54	n.s.
Oxcarbazepine	300	20	5	10	2	n.s.

[a]Relative to original pill weight.
[b]Mann-Whitney U test.

(median of 280 mg dissolved, compared with 130 mg in the control model, $p<0.05$). The dissolution of haloperidol, oxcarbazepine, and methylphenidate did not vary between conditions. Five newer antipsychotics (clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) had greater dissolution in the control condition (Table 1).

DISCUSSION

Although the study design clearly was not definitive, it allowed, to our knowledge, the first exploration of psychiatric medication dissolution in the post-RYGB patient population. Future studies would do well to utilize more extensive and precise models of the human gastrointestinal tract or, more definitively, to assess serum concentrations and pharmacokinetics in the patients themselves to track post-RYGB changes. The dissolution data could provide a helpful starting point in the discussion of pharmacokinetics and eventually contribute to data-driven medication management in this growing patient population.

We are still far from fully understanding drug dissolution. Although dissolution data do not predict therapeutic efficacy, they can provide qualitative information about biologic availability. Because absorption is limited by the dissolution rate,[8] changes in dissolution can have a dramatic effect on the rate and/or extent of drug absorption. Several physiochemical processes are considered in determining the dissolution rate of drugs from solid forms under standardized conditions; these factors include the wetting characteristics of the solid dosage form, the penetration of the dissolution medium into the dosage form, the swelling process, disintegration, and de-aggregation. Solid dosage forms must undergo disintegration and de-aggregation to increase particle surface area and increase the rate of dissolution. Additional factors affecting drug dissolution include the physiochemical properties of the drug, the drug formulation, and the manufacturing process.[8]

Standardized dissolution tests attempt to mechanically recreate the physiologic environment in terms of time, temperature, agitation, and the characteristics of the dissolution medium.[5] The RYGB condition required a novel dissolution model, and, not surprisingly, there were some limitations to this model. Crushing the pills in the RYGB model reflected the common clinical practice among gastric bypass patients in the postoperative period. Pills are crushed because many medications have a coating to make them palatable, but the coating requires the presence of stomach acid to release the drug. Thus, the study design may have been biased toward greater dissolution in the RYGB model because of the increased surface area of the crushed pills. We accepted this bias in our study because of the close parallel with clinical usage.

It is important to note that a significant proportion of the undissolved remnant of crushed pills may have consisted of pill-coating material. We did not test the concentration of drug that was dissolved. If this were done, the solubility of psychiatric medications in the post-RYGB state could be better clarified.

This study confirmed the suspicion that solubility of psychiatric tablets is altered after gastric bypass, but it did not reveal differences in the absorption. To demonstrate a difference in the bioavailability of psychiatric medications after gastric bypass, a prospective clinical trial with monitoring of serum drug levels is required. Until these data are available, RYGB patients who require medication for psychiatric illnesses may require more diligent therapeutic monitoring to ensure correct dosing of their medications.

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