Pharmacokinetic Effects of Bariatric Surgery

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Pharmacokinetic Effects of Bariatric Surgery

Allan Edwards and Mary HH Ensom

OBJECTIVE: To evaluate the effect of bariatric surgery on the pharmacokinetics of medications.

DATA SOURCES: EMBASE (1980-September 2011), PubMed (1947-September 2011), MEDLINE (1948-September 2011), and *International Pharmaceutical Abstracts* (1970-September 2011) were searched for the following terms: gastric bypass or stomach bypass or bariatric surgery, and pharmacokinetic.

STUDY SELECTION AND DATA EXTRACTION: All English-language primary literature that reported pharmacokinetic parameters for orally dosed medications in post–bariatric surgery patients was evaluated, with the exception of studies involving the jejunoileal bypass method.

DATA SYNTHESIS: Worldwide, the incidence of obesity is increasing and so are options for managing it, including bariatric surgery. Major alterations to the physical structure of the gastrointestinal tract may cause changes in pharmacokinetic parameters of oral medications, which theoretically could lead to increased or decreased drug exposure. We reviewed 11 prospective trials, 5 of which were available only as abstracts and all of which were small with relatively low power (n = 6-36). The studies were split almost equally between using subjects as their own controls or using separate control subjects; 1 study used historical data as the control. Results were varied, highlighting the multifactorial nature of pharmacokinetics. Drugs such as atorvastatin, which undergo presystemic intestinal metabolism via CYP3A, may show increased bioavailability, whereas those such as amoxicillin, which rely on transport mediators, may be decreased. Most of the studies lacked sufficient power to show significant changes in post–bariatric surgery patients.

CONCLUSIONS: Bariatric surgical procedures may result in altered pharmacokinetic parameters, but the literature is lacking in sufficient quantity and quality of studies to make solid conclusions and recommendations. Until more studies of sufficient power are completed, clinicians should closely monitor these patients in the immediate and distant postsurgical period for signs of both drug efficacy and toxicity and adjust their medications as required.

KEY WORDS: bariatric surgery, gastric bypass, pharmacokinetics, stomach bypass.

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Request

Do patients who have undergone bariatric surgery procedures display altered pharmacokinetics?

Response

BACKGROUND

The prevalence of obesity has reached a level that many are calling an epidemic. The World Health Organization estimated that, as of 2008, there were 1.5 billion overweight adults worldwide, with >500 million classified as morbidly obese.[1] Increased body mass index (BMI) has been linked to increased risk of multiple chronic diseases, with increasing risk as BMI rises.[1] A BMI increase of 5 kg/m^2 is associated with increased overall mortality of 30%, particularly related to vascular disease.[2]

Lack of success with lifestyle modifications is leading more patients to turn to medical and surgical solutions for weight management. Bariatric surgery is an effective method of inducing weight loss, resolves type 2 diabetes in 73-90% of patients, and reduces risk of developing coronary artery disease by half.[3] Hence, the number of bariatric surgical proce-

Author information provided at end of text.

dures performed in the US has risen annually since 1990[4]; with >15 million morbidly obese people, approximately 220,000 bariatric surgeries were performed in 2009.[3]

Bariatric surgery produces weight loss through 2 general mechanisms: restriction by creating a gastric pouch smaller than the stomach, resulting in a feeling of satiety with less food consumed, and malabsorption by redirecting the alimentary limb to bypass the proximal small intestine.[3] There are 2 common surgical methods resulting in malabsorption: Roux-en-Y gastric bypass (gastric bypass procedure; GBP) in which the stomach size is greatly reduced and then reattached to the middle of the small intestine, bypassing the duodenum and 50-70 cm of the jejunum; and biliopancreatic diversion with duodenal switch (BPD-DS), in which a sleeve-shaped stomach is created and connected to the ileum, bypassing 60% of the small intestine.[3,4] Bypassing the stomach and much of the small intestine could lead to changes in pharmacokinetics. Specifically, higher pH of the rerouted tract may result in less absorption of weakly acidic drugs or greater absorption of weakly basic ones; skipping the proximal small intestine removes a large surface area for absorption but also eliminates a site of high CYP3A intestinal first-pass metabolism.[4,5] Medications that require a protracted time for absorption, such as extended-release formulations, may display lower bioavailability, as may those that require gastrointestinal enzymes for either activation or absorption.[4] Bypassing an area of the small intestine with a high concentration of efflux transporters may have the effect of increasing bioavailability.[5] Because of the numerous factors affecting pharmacokinetics, these changes are difficult to predict and data on such changes exist for only a handful of medications.

LITERATURE REVIEW

EMBASE (1980-September 2011), PubMed (1947-September 2011), MEDLINE (1948-September 2011), and *International Pharmaceutical Abstracts* (1970-September 2011) were searched using the terms gastric bypass or stomach bypass or bariatric surgery, and pharmacokinetic. Primary literature reporting pharmacokinetic parameters for orally dosed medications in post–bariatric surgery patients was included, with the exception of studies involving jejunoileal bypass, which is no longer performed because of severe adverse events. The resulting 6 full articles (prospective studies) and 5 abstracts were reviewed (Table 1).[5-15]

Atorvastatin

Atorvastatin undergoes presystemic clearance via intestinal CYP3A (with low bioavailability of 12%) and is a substrate for P-glycoprotein.[16] Skottheim et al. investigated effects of bariatric surgery on atorvastatin's bioavailability in 2 studies.[5,6] The first was a prospective, open, controlled, nonrandomized, single-center study evaluating pharmacokinetics of atorvastatin in 15 subjects (aged >18 years) before and after (4-8 weeks) GBP.[5] Data for 3 patients were excluded due to indwelling catheter clotting (1) and deviating lengths of alimentary and biliopancreatic diversions (2). All subjects were on a statin prior to the study and, if it was not atorvastatin, were switched to atorvastatin at least 2 weeks prior to sampling. Patients were excluded if they were on other medications known to interact pharmacokinetically with atorvastatin. Results showed significant interpatient variability: 3 subjects with the highest preoperative exposure had decreases in area under the concentration-time curve (AUC) up to 2.9-fold, while 8 of 9 remaining subjects had a median 1.2-fold increase. On average, however, there was no significant difference in presurgical versus postsurgical $AUC_{0\text{-}8h}$ (50 vs 75 ng•h/mL; p = 0.99), maximum concentration (C_{max}) (28 vs 13 ng/mL; p = 0.83), or time to C_{max} (t_{max}) (1.6 vs 1.8 h; p = 0.39). Although the study was well conducted, using patients as their own controls and employing appropriate sampling times and validated analytical methods displaying acceptable accuracy and precision, it was limited by low power (eg, losing 20% of their subject data) to detect significant differences.

Their second study (N = 10) was of similar design and inclusion/exclusion criteria but patients underwent BPD-DS instead of GBP.[6] Results showed significantly increased postsurgical atorvastatin $AUC_{0\text{-}8h}$ (30 ± 22.1 before surgery vs 43 ± 37.7 ng•h/mL after surgery; p = 0.001), C_{max} (20 ± 24.0 vs 28 ± 22.5 ng/mL; p = 0.04), and t_{max} (1.2 ± 0.8 vs 2.3 ± 1.0 h; p = 0.03). This corresponded to a mean 2-fold increase in AUC (range 1.0-4.2; p = 0.001) and 2.2-fold increase in C_{max} (range 0.5-6.2; p = 0.04). The marked increase in bioavailability may appear unexpected (eg, bypassing large absorptive area of small intestine) but emphasizes the impact of intestinal CYP3A presystemic metabolism. The subdued increase in bioavailability in GBP patients, with increased exposure to their small intestine, lends further support to this hypothesis. Study limitations of this trial were small sample size and, with only 1 sample taken after surgery, inability to characterize time course for altered bioavailability. Yet unknown is whether adaptations occur during the initial year after the procedure that return bioavailability toward presurgical levels.

Metformin

Bariatric surgery is frequently used in patients with diabetes not only to control obesity but also to restore glycemic control.[3] Recognizing that over 40% of bariatric surgery patients will redevelop diabetes, Padwal et al. published a trial studying the pharmacokinetic changes of metformin in GBP patients 3 or more months after surgery, as

Table 1. Summary of Clinical Studies on Bariatric Surgery

Medication	Pts.	Pharmacokinetic Change	Proposed Mechanism of Pharmacokinetic Change	Strengths/ Limitations
Atorvastatin[5,6]	N = 12; pre- and post-Roux-en-Y[5]	No significant changes	None	Strength: subjects as own controls; appropriate sampling and analytical design Limitation: power too low to detect differences
	N = 10; pre- and post-biliopancreatic diversion with duodenal switch[6]	↑ AUC, ↑ C_{max}, ↑ t_{max} postsurgery	Decreased presystemic metabolism by bypassing intestinal CYP3A	Strength: subjects as own controls Limitation: small sample size; unknown if change persists beyond initial postsurgical period
Metformin[7]	N = 32; 16 Roux-en-Y pts. vs 16 BMI-matched controls	↑ Bioavailability (%), ↑ V_d, ↑ Cl in surgical cohort; ↔ AUC, C_{max}, t_{max}; metformin levels not correlated with glucose levels	Delayed gastric emptying increasing intestinal transit time; upregulation of active transporters postsurgery	Strength: matched controls; examined pharmacodynamic effects; urine and plasma sampling Limitation: small sample size; no explanation for for V_d change; single-dose study did not assess clinical steady-state condition
Sertraline[8]	N = 10; 5 female Roux-en-Y pts. vs 5 matched controls	↓ AUC, ↓ C_{max} in surgical cohort	Loss of absorptive surface area outweighed bypassing intestinal CYP3A	Strength: significant results achieved Limitation: short sampling time (10.5 hours), considering $t_{1/2}$ of 24-26 hours
Tacrolimus[9]	Open-label; 6 Roux-en-Y pts., pre- (4) and posttransplant (2) vs 51 historical controls	↓ AUC, ↓ C_{max}, ↓ AUC-to-dose ratio, ↓ t_{max} in surgical group	Loss of absorptive surface area	Strength: none Limitation: wide variability in data; historical controls on various dosing regimens; underpowered to show meaningful result
Sirolimus[9]	Same as tacrolimus	↓ AUC, ↓ AUC-to-dose ratio	Loss of absorptive surface area	Same as tacrolimus
Mycophenolate[9]	Same as tacrolimus	↓ AUC	Not stated	Same as tacrolimus
Ethanol[10]	Open-label; 12 female Roux-en-Y pts. vs 12 controls	↑ C_{max}, ↓ t_{max}, ↔ AUC in surgical group	Rapid delivery to highly absorptive area of jejunum	Strength: appropriate sampling strategy; matched controls Limitation: chronic alcohol users not studied
Morphine[11]	N = 6; pre- and post-Roux-en-Y	↑ C_{max}, ↔ AUC, ↓ t_{max}	Rapid delivery to highly absorptive area of jejunum	Strength: subjects as own controls Limitation: abstract only; small sample size
Levothyroxine[12]	Open-label; 15 Roux-en-Y pts. vs 15 controls	No significant kinetic changes, but TSH significantly ↓ in surgical group	No explanation given for change in TSH	Strength: matched controls Limitation: abstract only
Acetaminophen[13,14]	N = 8; pre- and post-Roux-en-Y, followed 1 week post-procedure[13]	No significant changes	None	Strength: subjects as own controls Limitation: small sample size
	N = 12; pre- and post-Roux-en-Y; followed at 1 year post-procedure[14]	↑ AUC, ↑ C_{max} post-surgical at 1 year	Adaptation in gastrointestinal tract compensating for loss of absorptive surface area	Strength: subjects as own controls; followed at 1 year Limitation: small sample size; no data between 1 week postprocedure and 1 year
Talinolol[13,14]	Same as acetaminophen[13]	No significant changes	None	Same as acetaminophen
	Same as acetaminophen[14]	No significant changes	None	Same as acetaminophen
Amoxicillin[13,14]	Same as acetaminophen[13]	↑ C_{max}, ↔ AUC, ↔ t_{max}	No explanation given	Same as acetaminophen
	Same as acetaminophen[14]	No significant changes	None	Same as acetaminophen
Caffeine[15]	N = 36; 18 Roux-en-Y pts. at least 1 year postsurgery vs 18 matched controls	↓ t_{max}, ↔ AUC, ↔ C_{max} in surgical cohort	No explanation given	Strength: substrates for 4 cytochrome P450 isoforms examined; largest study to date; pts. long past surgery Limitation: questionable conclusion that ↓ t_{max} related to cytochrome P450 activity; most of the drugs studied not commonly used in outpatient practice
Tolbutamide[15]	Same as caffeine	↓ t_{max}, ↔ AUC, ↔ C_{max} in surgical cohort	No explanation given	Same as caffeine
Omeprazole[15]	Same as caffeine	↓ t_{max}, ↔ AUC, ↔ C_{max} in surgical cohort	No explanation given	Same as caffeine
Oral midazolam[15]	Same as caffeine	↓ t_{max}, ↔ AUC, ↔ C_{max} in surgical cohort	No explanation given	Same as caffeine

AUC = area under the concentration versus time curved; BMI = body mass index; Cl = clearance; C_{max} = maximum concentration; $t_{1/2}$ = half-life; t_{max} = time to C_{max}; TSH = thyroid-stimulating hormone; V_d = volume of distribution.

well as the $AUC_{0\text{-}8h}$ of plasma glucose to determine clinical impact of any differences found.[7] Metformin is a substrate for plasma membrane monoamine transporters in the intestinal tract and the investigators hypothesized that surgically bypassing a significant area for absorption would reduce metformin absorption in these patients. Estimating that 13 patients would be required to detect a 30% difference in AUC between the groups, they enrolled 16 subjects and 16 matched controls to allow for variations in the estimate. After administering 1 g of metformin hydrochloride, plasma metformin and glucose samples were drawn for 8 hours and urine collected for 24 hours. Caloric intake was controlled via standardized meals and snacks.

Contrary to expectations, bioavailability of metformin was significantly higher in the GBP cohort, at 41.8%, vs 27.8% in the controls (mean difference 14.0%, 95% CI 4.1 to 23.9; p = 0.007). However, this increase in absorption did not lead to significant differences in AUC, C_{max}, or t_{max}. More surprising was the discovery of increased renal clearance (461 vs 337 mL/min; p = 0.047) and volume of distribution (1.4 vs 1.0 L/kg; p = 0.02) in the GBP patients compared to controls. The pharmacodynamics study did show significantly lowered glucose $AUC_{0\text{-}8h}$ in the surgical group (35.8 vs 41.7 mmol/mL/h; mean difference 5.9 mmol/mL/h, 95% CI 3.1 to 8.8; p = 0.0002) but multivariate linear analysis did not show a correlation between this value and $AUC_{0\text{-}\infty}$ of metformin. Rather, fasting glucose levels at baseline were the strongest predictor of glucose $AUC_{0\text{-}8h}$.[7]

The authors presented 2 possible explanations for the increased bioavailability of metformin in GBP patients. Recognizing that Roux-en-Y gastric bypass with pouch volume 60-80 mL can cause delayed gastric emptying and increased intestinal transit time, it is possible that metformin was exposed to the remaining intestinal mucosa for a longer duration in the surgical subjects than in nonsurgical subjects, despite the intestinal distance being considerably smaller. Also, the absorption of metformin is dependent on plasma membrane monoamine transporter molecules, a saturable process; delayed gastric emptying may decrease the rate at which the drug enters the intestine and prevent transporter saturation. Their second hypothesis was that, in response to the loss of intestinal area, transporter may be upregulated in GBP patients and thus increase absorption. An explanation for the changes in renal clearance and volume of distribution was not provided. Overall, this study did not address the clinical effects that could occur with steady-state levels of metformin.[7]

Sertraline

Citing high incidence of depression and antidepressant use in obese patients that continues after bariatric surgery, Roerig et al. designed a small trial comparing sertraline pharmacokinetics in GBP versus nonsurgical patients.[8] Similar to atorvastatin,[16] sertraline is metabolized by cytochrome P450 enzymes and therefore may also display increased absorption after surgery. Following administration of sertraline 100 mg to 5 female GBP patients and 5 matched nonsurgical controls, serial blood sampling (10.5 hours) was performed.[8] Results supported the authors' hypothesis that loss of absorptive area has a greater impact on sertraline pharmacokinetics than a potential decrease in intestinal presystemic metabolism: $AUC_{0\text{-}10.5h}$ in the surgical cohort was 124.45 ± 55.46 ng•h/mL, compared to 314.80 ± 129.56 ng•h/mL in controls (p = 0.043); C_{max} was also lower in the GBP group (19.03 ± 7.79 vs 48.73 ± 19.12 ng/mL; p = 0.043). Differences in t_{max} were not significant.

While limited by a small, single-sex sample, the significant differences observed should prompt clinicians to reevaluate sertraline's effectiveness in female patients during the postoperative phase. Another limitation of this trial is the short sampling time (10.5 hours), in light of sertraline's 24- to 26-hour half-life.[8]

Immunosuppressants (Tacrolimus, Sirolimus, and Mycophenolate)

An open-label, historically controlled, nonrandomized, single-center trial investigated the pharmacokinetics of tacrolimus, sirolimus, and mycophenolate mofetil (MMF) in either renal transplant recipients or patients with end-stage renal disease (ESRD) awaiting transplant, who had previously undergone GBP (n = 6).[9] All ESRD patients received the same oral regimen of sirolimus 6 mg at 0800 and mycophenolate mofetil 1 g and tacrolimus 4 mg at 0800 and 2000 for 1 day prior to sampling. The 2 transplant subjects remained on their normal doses. Serial postdose samples for sirolimus (24 hours) and for both doses of mycophenolate mofetil and tacrolimus (12 hours) were analyzed using previously validated assays. Unfortunately, numerous samples could not be analyzed because of improper handling. Also, one ESRD subject lost intravenous access after the second tacrolimus dose.

Of note, the historical controls (n = 51) received sirolimus oral solution and therefore had higher C_{max} (32.2 ± 8.9 vs 18.2 ± 11.5 µg/L) and faster t_{max} values (0.7 ± 0.3 vs 2.0 ± 0.7 hours) than GBP subjects receiving tablets. Exposure to sirolimus was also lower in the bypass population, as seen in $AUC_{0\text{-}\infty}$ (181.1 ± 121.7 vs 335 ± 136 µg•h/L for controls receiving 3 mg/m² [5.82 mg average]; AUC-to-dose ratio 30.2 ± 20.3 vs 57.5 ± 23.4). Comparing results for tacrolimus to published pharmacokinetic data yielded similar findings: the bypass group had lower C_{max} (15.8 ± 6.6 vs 23.2 µg/L), $AUC_{0\text{-}\infty}$ (71.1 ± 29.2 vs 269.6 µg•h/L), and AUC-to-dose ratio (17.8 vs 53.92) values, and shorter t_{max} (1.3 ± 0.5 vs 2.0 hours), with the bypass group receiving a lower average dose (0.42 mg/kg) compared to controls (0.66 mg/kg). For mycophenolic acid (the active form

of MMF), only AUC_{0-12} was reported for GBP patients (42.7 ± 9.2 ng•h/L). It was lower compared to that for controls in the general transplant population (65.3 ng•h/L), although the dose given to controls was not reported.[9]

Wide variability in data and low power present challenges in applying the findings of this study to other patient groups. The other major limitation was using historical data for the control, as dosing regimens were not equivalent between groups, nor were sampling strategies or analytical methods used to generate pharmacokinetic data. While it is interesting that all 3 medications displayed lower bioavailability in GBP subjects compared to controls, this finding may have been due strictly to chance.[9]

Ethanol

Following reports of increased sensitivity to alcohol after bariatric surgery, Klockhoff et al. studied the pharmacokinetics of ethanol in 12 women who underwent GBP, compared to 12 non-bypass subjects of similar BMI (26.9 ± 4.0 vs 28.2 ± 3.76 kg/m², respectively).[10] After orange juice containing 0.3 g/kg of pure ethanol was administered to fasting subjects, blood samples were drawn every 10 minutes for 3.5 hours. The AUC for the GBP group was similar to that of controls (56.1 ± 12.8 vs 54.6 ± 10.2 g•min/L, respectively), but C_{max} and t_{max} values were higher/faster for bypass patients (0.741 ± 0.211 vs 0.577 ± 0.112 g/L and 10 [range 10-20] vs 30 [20-50] min, respectively). Blood alcohol concentration was higher only in GBP patients for 30 minutes after the dose, suggesting that faster t_{max} is due to more rapid transit of ethanol into the highly absorptive jejunum. This rapid absorption could explain the perceived increased alcohol sensitivity experienced by some post-bypass patients and prompts further investigation into similar effects with other potential drugs of abuse (eg, opioids). The main study limitation is lack of data on chronic users of alcohol.

Morphine

An abstract describing a pharmacokinetic study of 6 subjects given oral morphine 30 mg before and after GBP showed a significantly increased C_{max} after surgery (16.8 ± 10.1 vs 22 ± 13.5 ng/mL; p = 0.02), as well as a higher plasma concentration at 0.5 h.[11] As with the ethanol study,[10] $AUC_{0-\infty}$ and $t_{1/2}$ were not significantly different before and after surgery, suggesting that faster absorption occurred due to rapid transfer of drug to the jejunum.[11] t_{max} Appeared to be shorter postsurgery (0.5 vs 1.0 hours; p value not given).

Levothyroxine

Rubio et al. studied levothyroxine in 15 GBP and 15 non-bypass obese subjects.[12] Because levothyroxine depends on dissolution in an acidic environment, investigators postulated that absorption would be decreased in surgical patients. Following a single 600-µg dose, there was no difference in mean levothyroxine absorption, AUC, C_{max}, or t_{max} between the 2 groups, but serum thyroid-stimulating hormone levels were significantly higher in the nonsurgical group. Insufficient information was presented to render conclusions as to why thyroid-stimulating hormone levels were different despite similar pharmacokinetic values.

Acetaminophen, Talinolol, and Amoxicillin

Oswald et al. completed 2 similar 3-period, crossover studies evaluating acetaminophen (well absorbed through the gastrointestinal tract), talinolol (P-glycoprotein substrate), and amoxicillin (peptide transporter-1 substrate) in patients before and after GBP.[13,14] While investigators expected decreased talinolol and amoxicillin absorption after surgery, the first study (n = 8) showed no significant differences between the pre- and postsurgery periods except for the C_{max} of amoxicillin (2.57 ± 1.51 vs 3.84 ± 1.45 µg/mL, respectively; p = 0.036).[13] Although the AUC_{0-24h} for both drugs and C_{max} for amoxicillin appeared lower, these did not reach statistical significance. In the second study (n = 12), subjects' blood concentrations were measured 1 week after the procedure and again after 1 year.[14] Contrary to previous results, no statistically significant differences after 1 week occurred for any drug. More interesting is that after 1 year, acetaminophen AUC and C_{max} were significantly increased compared to presurgical levels. Although the mechanism is unclear, it is possible that, in response to a state of decreased absorption, adaptations to the gastrointestinal tract occurred during the postoperative phase that increased absorption beyond prebypass levels. It remains to be seen whether this phenomenon will occur with other drugs or nutrients.

Caffeine, Tolbutamide, Omeprazole, and Midazolam

As discussed above, bypassing areas of intestinal cytochrome P450 isoforms could lead to changes in drug bioavailability. In an attempt to examine this further, Tandra et al. administered substrates of intestinal CYP1A2 (caffeine), CYP2C9 (tolbutamide), CYP2C19 (omeprazole), and CYP3A (midazolam) as an oral cocktail to 18 GBP patients more than 1 year after surgery, as well as to 18 matched controls.[15] Measurement of the AUC ratio between parent drug and metabolite demonstrated no statistically significant difference between either group for all 4 drugs, nor was there a significant difference in C_{max}, suggesting that these cytochrome P450 isoforms are not appreciably affected by GBP. There was, however, a significantly shorter t_{max} in GBP patients for all 4 substrates. While this is likely due to faster transition from the gastric pouch to areas of higher absorption, the authors did not provide an explanation beyond stating that substrates for

these cytochrome P450 isoforms are more rapidly absorbed in bypass patients.

Summary

As global rates of obesity continue to rise, so too will the number of patients undergoing bariatric surgery. The literature is lacking studies investigating alterations in pharmacokinetics in these patients, as data could be found for only 15 medications plus ethanol. The available evidence is also difficult to interpret, as repeated studies on some medications have demonstrated conflicting results indicating that changes do occur and are not always predictable or consistent. The use of inappropriate or comparison data makes measuring the magnitude of possible changes in pharmacokinetic data problematic, and all of the studies available suffer from small sample sizes. Clinicians are also challenged by attempting to link clinical significance to statistical significance.

Clinicians should be aware that they will see more patients who have had bariatric surgery and an assessment of medication regimens in such patients is warranted. Clearly, multiple mechanisms can affect bioavailability, including shifts in gastric pH and gastrointestinal transit time, as well as exposure to metabolic enzymes and efflux and absorption transporters. Until more studies of sufficient power to detect true differences are completed, particularly on medications with a narrow therapeutic index or significant toxicities, clinicians should gain knowledge of the surgical procedures involved, the length of absorptive surface area lost, and specific absorptive properties of the drugs in question so that they can form a logical hypothesis. The final step is to continually monitor patients clinically for efficacy and toxicity and adjust doses as required.

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Efectos Farmacocinéticos de la Cirugía Bariátrica

A Edwards y MHH Ensom

Ann Pharmacother 2012;46:130-6.

EXTRACTO

OBJETIVO: Evaluar el efecto de la cirugía bariátrica en la farmacocinética de los medicamentos.

FUENTES DE INFORMACIÓN: Búsqueda bibliográfica en EMBASE (1980-septiembre 2011), PubMed (1947-septiembre 2011), MEDLINE (1948-septiembre 2011) e *Abstractos Farmacéuticos Internacionales* (1970-septiembre 2011) con los siguientes términos: bypass gástrico, bypass estomacal, cirugía bariátrica, y farmacocinética.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Toda la literatura primaria en inglés que reportaron parámetros farmacocinéticos para medicamentos de administración oral en pacientes que habían sido sometidos a cirugía bariátrica, con excepción de estudios que involucraron el bypass yeyunoileal.

SÍNTESIS: Mundialmente, la incidencia de obesidad está aumentando, y de igual manera aumentan las opciones para manejarla. Una de estas opciones es la cirugía bariátrica. Alteraciones mayores en la estructura física del trayecto gastrointestinal puede ocasionar cambios en los parámetros farmacocinéticos de medicamentos orales, lo cual teóricamente podría llevar a aumentar o disminuir la exposición al medicamento. Revisamos 11 estudios prospectivos, 5 de los cuales estaban sólo disponibles como resúmenes. Todos los estudios eran pequeños, con un poder estadístico bajo (n = 6 a 36). Los estudios estaban distribuidos igualmente en el uso de participantes como sus propios controles o usar otros participantes como controles; uno usó datos históricos como control. Los resultados fueron variados, destacándo la naturaleza multifactorial de la farmacocinética. Medicamentos como la atorvastatina, la cual tiene un metabolismo intestinal pre-sistémico mediante el citocromo P450 3A (CYP3A), puede demostrar aumento en biodisponibilidad, mientras en otros como la amoxicilina, la cual depende de mediadores de transporte, puede disminuir. La mayoría de los estudios carecieron de poder estadístico para demostrar cambios significativos en pacientes port-quirúrgicos.

CONCLUSIONES: Los procedimientos quirúrgicos bariátricos pueden resultar en la alteración de parámetros farmacocinéticos pero la literatura carece de una cantidad suficiente de estudios de calidad suficiente como para hacer recomendaciones y recomendaciones sólidas. Hasta que se realicen más estudios que tengan suficiente poder estadístico, los clínicos deben monitorear de cerca estos pacientes durante los períodos inmediatos y distantes después de la cirugía para identificar señales de eficacia y toxicidad y ajustar sus medicamentos según requerido.

Traducido por Homero A Monsanto

Les Effets de la Chirurgie Bariatrique sur la Pharmacocinétique des Médicaments

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RÉSUMÉ

OBJECTIF: Évaluer l'effet de la chirurgie bariatrique sur la pharmacocinétique des médicaments.

SOURCES DE DONNÉES: Une recherche de la documentation scientifique a été effectuée à l'aide de EMBASE (1980 – septembre 2011), PubMed (1947 – septembre 2011), MEDLINE (1948 – septembre 2011) et l'*International Pharmaceutique Résumé* (1970 – septembre 2011) et des termes suivants: dérivation gastrique, dérivation de l'estomac ou chirurgie bariatrique, et pharmacocinétique.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Toute la documentation scientifique de langue anglaise faisant mention de paramètres pharmacocinétiques pour des médicaments administrés par voie orale pour des patients ayant subi une chirurgie bariatrique a été évaluée à l'exception des études impliquant la procédure chirurgicale de dérivation jéjuno-iléale.

SYNTHÈSE DES DONNÉES: L'incidence de l'obésité est en augmentation à travers le monde et également les options pour sa prise en charge, incluant la chirurgie bariatrique. Des altérations majeures à la structure physique du tractus gastro-intestinal peuvent causer des changements dans les paramètres pharmacocinétiques des médicaments administrés par voie orale qui théoriquement peuvent conduire à une augmentation ou une diminution de l'exposition du médicament. Onze études prospectives ont été évaluées, dont 5 disponibles seulement sous forme de résumés et toutes avec une population de faible envergure (n = 6 à 36). Les études étaient divisées en part égal soient celles utilisant les sujets comme leur propre contrôle ou des sujets séparés; une étude utilisait des données historiques comme groupe contrôle. Les résultats étaient variés, rehaussant la nature multifactorielle des paramètres pharmacocinétiques. Les médicaments tels que l'atorvastatine, qui subit un métabolisme intestinal pré-systémique par le biais du cytochrome P450 3A (CYP3A), pourrait résulter en une augmentation de sa biodisponibilité. D'autres médicaments tels que l'amoxicilline, qui s'appuie sur des médiateurs pour son transport, pourrait démontrer une biodisponibilité moindre. La plupart des études affichaient un nombre de patients insuffisant pour pouvoir démontrer des changements significatifs à la suite de la chirurgie bariatrique.

CONCLUSIONS: Les procédures chirurgicales bariatriques peuvent causer des altérations au niveau des paramètres pharmacocinétiques mais le peu de documentation scientifique disponible à ce jour et la qualité de ces études ne permettent pas de tirer des conclusions solides et des recommandations. En attente d'études complétées plus robustes, les cliniciens devraient faire un suivi étroit de ces patients durant la période suivant la chirurgie et ultérieurement pour détecter des signes d'efficacité ou de toxicité et ajuster la médication des patients en fonction de ces signaux.

Traduit par Chantal Guévremont