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BÁRBARA LETÍCIA DA SILVA GUEDES

PACIENTES SUBMETIDOS À CIRURGIA BARIÁTRICA ROUX-EM-Y: PERFIL DE PRESCRIÇÃO DE MEDICAMENTOS E DISSOLUÇÃO DE FORMAS FARMACÊUTICAS SÓLIDAS ORAIS EM AMBIENTE SIMULADO

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Dissertação apresentada ao Programa de Pós-Graduação em Biociências e Fisiopatologia do Departamento de Análises Clínicas e Biomedicina, Centro de Ciências da Saúde da Universidade Estadual de Maringá, como requisito parcial para obtenção do título de Mestre em Biociências e Fisiopatologia.
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Universidade Estadual de Maringá

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University of Southern California

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EPÍGRAFE

Don't only practice your art, but force your way into its secrets, for it and knowledge can raise men to the Divine.

Ludwig van Beethoven

Pacientes submetidos à Cirurgia Bariátrica Roux-em-Y: Perfil de Prescrição de Medicamentos e Dissolução de formas farmacêuticas sólidas orais em ambiente simulado

Resumo

A realização de Cirurgia Bariátrica tem crescido exponencialmente no Brasil e no mundo nos últimos dez anos e o Bypass Gástrico em Y de Roux (RYGB) tem sido o procedimento mais bem sucedido para perda de peso. Devido às alterações anatômicas no trato gastrintestinal, a administração de formas farmacêuticas orais pode ser uma preocupação por causa do desvio do estômago e duodeno, o qual pode alterar a taxa de dissolução de comprimidos e cápsulas e a consequente absorção do fármaco. Para evitar falhas terapêuticas e para segurança do paciente, mudar as formas farmacêuticas sólidas para formulações líquidas ou mastigáveis pode ser recomendado para esses pacientes. Assim, o objetivo deste estudo foi investigar o comportamento prescritivo de profissionais de saúde não bariátricos para esses pacientes e por quais referências se orientam para prescrição; os problemas farmacoterapêuticos pós-cirurgia com os pacientes e a simulação da dissolução de antibióticos, antivirais e anti-hipertensivos no modelo pós-bariátrico. Dois questionários validados foram utilizados para entrevistar profissionais e pacientes e um modelo *in vitro* de dissolução foi desenvolvido para simular o pequeno compartimento remanescente do estômago. Os resultados foram divididos em dois artigos. O primeiro, "Decision making for prescription of medicines for bariatric surgery" relata que a maioria dos profissionais entrevistados não fornece orientações clínicas específicas para esses indivíduos, mas 52% acredita que o RYGB interfere na absorção de fármacos e 55% observaram falha terapêutica com esses pacientes apesar de apenas 16% confirmar que a falha deveu-se a problemas de absorção. Em relação à variável experiência profissional, os prescritores com 10 anos ou mais apresentaram 5,88 vezes maior tendência a prescrever comprimidos ou cápsulas sem recomendações específicas ou alterar para uma forma farmacêutica mais adequada a esses pacientes, porém, foram 3,85 vezes mais propensos a realizar acompanhamento com os pacientes do que os profissionais mais novos. O segundo artigo, "Evidences that bioavailability of some highly soluble drugs are unaltered in Roux-en-Y bariatric patients", compara os resultados do teste de dissolução modificado aos dados da literatura, demonstrando evidências de que fármacos altamente solúveis não apresentam a taxa de dissolução alterada devido ao procedimento de RYGB. A maioria dos estudos de biodisponibilidade diminuída envolvem fármacos de classe biofarmacêutica II ou IV, enquanto que as classes I e III demonstram biodisponibilidade inalterada.

Palavras chave: cirurgia bariátrica, obesidade, biodisponibilidade, farmacocinética, farmacoterapia.

Patients undergone Roux-en-Y Bariatric Surgery: Prescription Profile of Medicines and Dissolution of solid oral dosage forms in simulated environment

ABSTRACT

Bariatric Surgeries have grown exponentially worldwide and in Brazil in the last ten years and the Roux-en-Y Gastric Bypass (RYGB) has been one the most successful surgical procedures to lead the weight loss. Because the anatomical changes in the gastrointestinal tract, the administration of oral dosage forms may be a concern because the bypassing the stomach and duodenum may alter the dissolution rate of tablets and capsules and further drug absorption. To avoid therapeutic failure and for the safety of these patients, changing solid oral dosages for liquid or chewable dosage forms should be recommended for these patients. So, the aim of this study was to investigate the prescription behavior of non-bariatric health providers for bariatric patients and which sources of information they follow to prescribe, the post-surgery pharmacotherapeutic problems with this population and to simulate the dissolution test for antibiotic, antiviral and antihypertensive drugs in post-bariatric model. Two validated questionnaires were used to interview health providers and patients and a modified *in vitro* dissolution test was developed to simulate the small pouch of the stomach. The results were divided into two articles. The first, "Decision making for prescription of medicines for bariatric surgery" reports that most of the interviewed providers do not provide specific clinical recommendation for these patients, but 52% believe that RYGB interfere in the drug absorption and 55% of them had seen therapeutic failure in bariatric patients but only 16% confirmed that it was because absorption problem. Regarding the variable of work experience, providers older than 10 years of professional experience were 5.88 times more likely to prescribe tablets or capsules without specific recommendation or change for other more suitable dosage forms for these patients but they are 3.85 times more likely to perform follow up with patients than younger providers. The second article, "Some evidences that bioavailability of some highly soluble drugs are unaltered in Roux-en-Y bariatric patients" compares the results from modified dissolution test with data from the literature showing evidences that highly soluble drugs dissolution rate are not altered because the RYGB surgery. Most of decreased bioavailability studies involved BCS class II or IV drugs, while, class I or III presented unaltered bioavailability.

Keywords: bariatric surgery, obesity, bioavailability, pharmacokinetics, pharmacotherapy.

Dissertação elaborada e formatada conforme as normas das publicações científicas: *Patient Education and Counseling* (artigo 1) Disponível em: http://goo.gl/NKzcmd e *Surgery for Obesity and Related Deseases* (artigo 2) Disponível em: http://goo.gl/e0Upnn

SUMÁRIO

CAPÍTULO I

INTRODUÇÃO

O excesso de peso e a obesidade representam o sexto maior fator de risco de saúde atual para a população mundial e têm alcançado proporções epidêmicas [1]. Esse fator tem aumentado a demanda por cirurgias bariátricas também no Brasil [1,2]. Esta opção terapêutica tem sido escolhida principalmente devido à confirmação de sucesso na remissão de quadros de comorbidade [3,4,5].

Embora muitas comorbidades melhorem após a cirurgia, alguns autores indicam a possibilidade do retorno do excesso de peso e de comorbidades ao longo dos anos, necessitando de novas intervenções farmacoterapêuticas [5], além da necessidade eventual do uso medicamentos em situações agudas e crônicas.

Quanto aos princípios técnicos, a cirurgia bariátrica vem sendo classificada em: a) Procedimentos Restritivos; b) Procedimentos Disabsortivos e c) Procedimentos Mistos.

Os procedimentos disabsortivos reduzem a absorção de calorias, proteínas e outros nutrientes; os restritivos diminuem a entrada de alimento e promovem rápida sensação de saciedade e a técnica mista é a combinação das anteriores. Na Figura 1 estão demonstradas, genericamente, as quatro diferentes modalidades de cirurgia bariátrica aprovadas no Brasil, com exceção do balão intragástrico, que não é considerado procedimento cirúrgico.

Entre as técnicas apresentadas, o *Bypass* Gástrico em Y de Roux (RYGB) (Figura 1C) é o procedimento mais utilizado nos EUA, Canadá e Brasil, e é considerado o padrão ouro para cirurgia bariátrica [6,7].

A remoção parcial do estômago e o bypass intestinal no procedimento RYGB levam a alterações nos fatores de absorção de nutrientes e fármacos, como a limitação na capacidade digestiva, diminuição do sítio de absorção, modificação do pH gástrico, redução ou ausência total do trânsito para absorção e metabolismo por enzimas e bombas de efluxo presentes ao longo do trato gastrintestinal (TGI) [8,9].

Além da absorção de nutrientes em geral, esse novo estado clínico pode afetar também o processo de absorção de um medicamento, que é dependente de características inerentes ao fármaco utilizado, como suas características físico-químicas, bem como das condições do TGI do indivíduo [10].

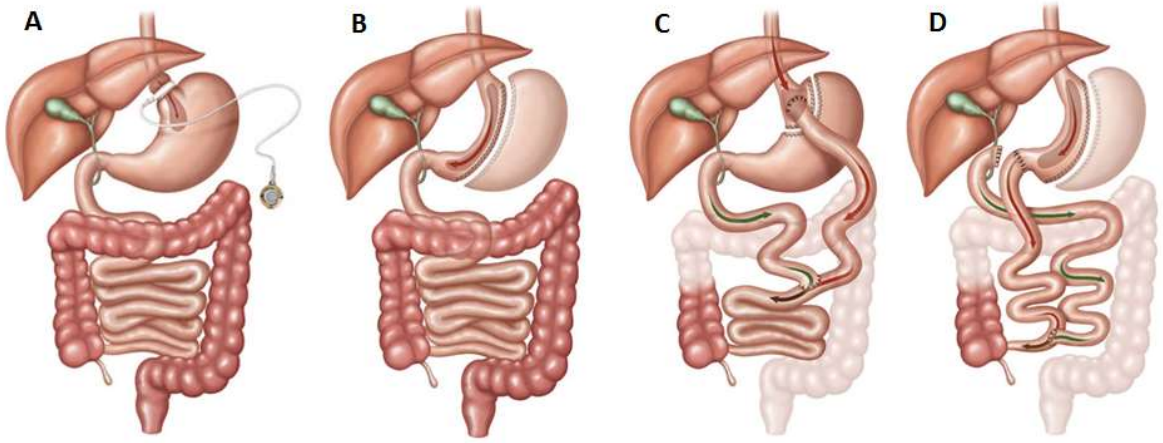

Figura 1. Técnicas cirúrgicas bariátricas. (A) Banda Gástrica Ajustável: instala-se um anel de silicone inflável ajustável ao estômago. (B) Gastrectomia Vertical: exclui-se parte do estômago reduzindo sua capacidade para 80 a 100 ml. (C) *Bypass* Gástrico em Y de Roux: procedimento misto em que o estômago é grampeado e cria-se um desvio para o segmento proximal do intestino. (D) Duodenal *Switch*: exclui-se parte do estômago e cria-se um desvio para o segmento distal do intestino. **Fonte**: Adaptado do site da Sociedade Brasileira de Cirurgia Bariátrica e Metabólica (SBCBM), disponível em: http://goo.gl/t5PfHk.

O conhecimento do processo de dissolução de uma forma farmacêutica disponibiliza informações úteis sobre a biodisponibilidade de um fármaco, uma vez que as formas farmacêuticas precisam se dissolver nos fluidos gastrintestinais para serem absorvidas. Dados de dissolução *in vitro* podem ser úteis na predição da biodisponibilidade *in vivo* [11,12] de alguns fármacos e não está completamente elucidado de que maneira fármacos com diferentes graus de solubilidade e permeabilidade sofrem interferência do ambiente gastrintestinal modificado.

O impacto desse rearranjo do TGI sobre a dissolução e a absorção de medicamentos sob formas comercialmente disponíveis necessita de investigação quanto aos níveis de segurança e efetividade, visando direcionar e orientar pacientes e prescritores nas suas orientações específicas.

Baseado nas propriedades de solubilidade, permeabilidade intestinal e dissolução, foi criado o Sistema de Classificação Biofarmacêutica (SCB) o qual classifica os fármacos em 4 classes: Classe I (Alta Solubilidade e Alta Permeabilidade), Classe II (Baixa Solubilidade e Alta Permeabilidade), Classe III (Alta Solubilidade e Baixa Permeabilidade) e Classe IV (Baixa Solubilidade e Baixa Permeabilidade) [12]. Adotado pela FDA (*Food and Drug Administration-EUA)*, OMS *(*Organização Mundial da Saúde) e EMA (Agência Européia de Medicamentos), o SCB vem sendo uma ferramenta regulatória para substituir estudos de bioequivalência por testes de dissolução *in vitro* para fármacos altamente solúveis e altamente permeáveis, racionalizando o desenvolvimento de produtos farmacêuticos e a introdução de

medicamentos genéricos no mercado, por reduzir a exposição de voluntários sadios aos fármacos-teste, os custos e tempo necessários aos processos de desenvolvimento de produtos farmacêuticos [13].

Assim, para fármacos de classe biofarmacêutica I, desde que apresentem também rápida dissolução, as entidades regulatórias de vários países propõem a isenção dos estudos de bioequivalência, uma vez que, nesses casos, o processo de absorção dependeria exclusivamente da capacidade/velocidade da forma farmacêutica em liberar o fármaco, já que devido à alta solubilidade, sua solubilização seria instantânea e, por sua alta permeabilidade, a absorção também seria instantânea. Nesses casos específicos a absorção do fármaco seria dependente somente da dissolução e da velocidade de esvaziamento gástrico do indivíduo. Portanto, fármacos de classe I podem ter a dispensa de estudos em humanos, sendo considerados bioisentos [11].

Entretanto, fármacos que apresentam janela terapêutica estreita e indicação terapêutica muito crítica e/ou que tenha grande número de falhas inexplicáveis na determinação da bioequivalência *in vivo* relatadas na literatura são, geralmente, não elegíveis para uma bioisenção [13].

Como os indivíduos submetidos à cirurgia bariátrica possuem um trato gastrintestinal bastante diferenciado, instala-se a dúvida sobre a veracidade dessas afirmativas para esses indivíduos. Sendo assim, o estudo de fármacos segundo o SCB e as prerrogativas clínicas que direcionam estudos de segurança de medicamentos devem ser revistos para se confirmar ou descartar as premissas seguidas para situações clínicas já conhecidas, nas quais o ambiente de dissolução e absorção não está afetado. Este dado é essencial para a otimização farmacoterapêutica dessa classe de pacientes.

Até o presente momento, apesar de não existirem guias com alto grau de evidências para o uso de medicamentos pós-cirurgia, algumas recomendações gerais sobre precauções para a administração de medicamentos tem sido realizadas [8,14,15,16]. Outras recomendações que partiram das alterações nutricionais já observadas levaram a elaboração de consensos clínicos e guias, bem como à necessidade de aconselhamento e acompanhamento nutricional com esses pacientes [6,7,8].

JUSTIFICATIVA

Além do considerável aumento da realização de cirurgia bariátrica, recentemente o Sistema Único de Saúde (SUS) indicou a realização desta cirurgia em pessoas com índice de

massa corporal (IMC) abaixo de 40 Kg/m^2 associado à comorbidades e autorizou a alteração da faixa etária em vigor, reduzindo a idade mínima de 18 para 16 anos e extinguindo a idade máxima de 65 anos, não havendo mais limite de idade para a realização do procedimento [17], dependendo estritamente das condições de saúde do candidato ao procedimento.

Apesar da expansão desta técnica, há poucos estudos avaliando o impacto da cirurgia na absorção de fármacos e consequentemente no efeito terapêutico; mesmo estudos *in vitro,* ou especialmente, envolvendo medicamentos de estreita margem terapêutica, de uso crônico ou cuja falha possa determinar piora no estado de saúde, internações e óbito, como antibióticos, antivirais e anti-hipertensivos.

OBJETIVOS

O objetivo deste estudo foi investigar: a) as ferramentas e fontes de referência utilizadas por médicos não cirurgiões bariátricos na prescrição para estes pacientes e as recomendações disponibilizadas aos pacientes para o uso de medicamentos; b) problemas farmacoterapêuticos que os pacientes possam apresentar pós-cirurgia e c) o perfil de dissolução de comprimidos e cápsulas de antibióticos, antivirais e anti-hipertensivos em ambiente simulado de Roux-em-Y.

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CAPÍTULO II

Artigo 1: “Decision-making for prescription of medicines for bariatric surgery”

DECISION-MAKING FOR PRESCRIPTION OF MEDICINES FOR BARIATRIC SURGERY

Bárbara Letícia da Silva Guedes[1], Maiara Camotti Montanha[2] Sergio Seiji Yamada[3], Sandra Regina Bin Silva[3], Daoud Nasser[4], Isolde Previdelli[5], Elza Kimura[6].

Abstract

Objective
To know the decision-making for prescribing oral dosage forms medicines for Roux-en-Y (RYGB) bariatric patients and provide evidence-based information to support the providers' decision making.

Methods
Two surveys were built to interview health providers and patients. In addition, a search in the main database was queried for reviewing pharmacokinetic studies involving bariatric surgery.

Results
Among 62 non-bariatric health providers, 52% believe RYGB interfere in the drug absorption, but 68% of them prescribe tablets as the first choice. Older providers are 5,9 times more likely to prescribe tablets than young providers, but they follow up the patients more than the young providers. Among 73 patients, only 24 had some health problems not related to the surgery and only 15 patients received some information about drug administration and most of journals cited by the providers had not pharmacokinetics studies involving bariatric surgery.

Conclusion
The most of the interviewed providers do not provide specific clinical recommendation to these individuals, although the most of interviewed patients had not problems related to medicines.

Practice Implication
As most of the providers did not attempt about the importance of the stomach and duodenum for drug prescription, this may represent a high risk for these population.

Keywords: *bariatric surgery, pharmacotherapy, prescription, questionnaires; bioavailability, pharmacokinetics, patient counseling.*

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[1] Post-Graduate Program in Bioscience and Physiopathology. State University of Maringa, Parana, Brazil.
[2] Undergraduate degree in Pharmacy. Pharmacy Department. State University of Maringa, Parana, Brazil.
[3] Regional University Hospital of Maringa. Clinical Research and Bioequivalence Nucleus, Maringa, PR, Brazil.
[4] Regional University Hospital of Maringa, Parana, Brazil.
[5] Statistical Department. State University of Maringa, PR.
[6] Pharmacy Department. Post-Graduate Program in Bioscience and Physiopathology. Clinical Research and Bioequivalence Nucleus, Maringa, Parana, Brazil.
Adress for correspondence: Prof.ªDr.ª Elza Kimura Grimshaw. Hospital Universitário Regional de Maringá, Núcleo de Pesquisa Clínica e Bioequivalência. Avenida Mandacarú, 1590, CEP: 87083-240, Maringa, Parana, Brazil. Phone number: 55 44 3011 9202, Email: elzakimura1@gmail.com

Universidade Estadual de Maringa Committee on Ethics in Research (COPEP, in portuguese). Registered on COPEP, nº 41908.

Decision-making for prescription of medicines for bariatric surgery

1. Introduction

Overweight and obesity represent the sixth largest risk factor for current health for the world population and has reached epidemic proportions. Parallel, the number of bariatric surgeries performed in Brazil has increased exponentially in the last ten years, from about 5000 procedures in 2000 to 60.000 in 2010 [1,2]. Furthermore, the National Health System (NHS) has just changed the rules allowing people from 16 years old to undertake bariatric surgery with a body mass index (BMI) above 40 kg/m^2, because the latest published results showing improvement in diabetes and other comorbidities associated to morbid obesity and consequently, reduce health care costs for this population [3].

After 10 years of bariatric surgery regulations in Brazil, there is no group evaluating the degree of absorption of oral medications in these patients and what are the implications in drug therapy, mainly in the Roux-en-Y gastric bypass (RYGB), which removes a considerable part of the stomach and duodenum, consisting among of the most successful techniques in weight loss [4,5]. The same way the nutritional deficiencies occur by reduction of the digestive tract, the amount and rate of absorption for some drugs may also be affected by the change in the gastrointestinal environment and release of active compounds from the pharmaceutical dosage forms [6,7,8].

The main concerns about absorption are about the solid dosage forms for these patients, once they need to be disintegrated and dissolved in a low volume [9] and low motility [10] before absorbed in the intestines. It is expected that once these dosage forms achieve the intestine, they will be absorbed but because the low motility and the volume of the stomach, the dissolution may be altered, reduced or delayed [11].

Theorical approaches using computational physiological models and systematic reviews have been carried out to show variation in the effect of medicines and

recommendations on how the patients should intake the solid oral dosage forms are suggested [4,12,13]. Also, several reviews explaining the surgery procedures [14,15,16,17] and nutritional implication [18-23] related to this population are available but no follow up was carried about problems with medicines in this population.

In order to carry out bariatric surgeries, the clinics and hospitals have to join a team of professionals, which include a surgeon, nurse, psychologist, physiotherapist or physical educator and nutritionist [24]. So, recommendation for nutritional supplementation, problems related to the bone loss and psychological problems are better established for these patients [18,19,21,22], but the problems with medicines and dose adjustments are not available and only few case reports have been published [4]. Furthermore, when the patients have some other health problems not related to the surgery, they are advised to find a non-bariatric specialist.

The success of therapy depends on the doctor/patient relationship within the consultation and according to the amount and type of information supplied by the patient for the provider and which question the doctors ask, the right decision for the therapeutic goal will be achieved [25]. Therefore, the specific content of the provider–patient conversation is crucial to the decision-making process.

For bariatric patients, as for any other type of surgery, before a consultation, a questionnaire is applied to all patients asking about previous surgeries, so the doctors should be aware of what type of bariatric surgery the patients underwent to make a right decision to prescribe the oral dosage forms medicines for this population.

So, in order to know how the non-bariatric doctors prescribe medicines for bariatric patients, which sources of information they use to prescribe and to complement their information, which type of information the bariatric patients receive from the providers for oral dosage forms administration this study was carried out. The main focus of our study was

to know how the decisions were made for prescribing oral dosage forms medicines for bariatric patients and provide evidence-based information about bioavailability of some drugs to support the providers' decision making.

2. Methods

Two surveys were built: one for the non-bariatric doctors and other for the bariatric patients. The protocol (number 41908) as well as the Informed Consent Term, was approved by the Local Ethics Committee before the study was carried out.

2.1. Data collection instrument

The measuring instrument was developed based on procedures for constructing psychological scales [26]. The face validity, content validity and internal consistency of the instrument were analyzed. Through theoretical elucidation 16 questions for health providers and 22 questions for the patients were built.

The face validity and content validity was judged by a panel of six field experts, including physicians, nurses and pharmacists, and the internal consistency was measured by a pre-test conducted with providers and individuals following bariatric surgery, which were not included in the study sample. The "experts", based on the "Analysis Guide of the Psychometric Properties of the Questionnaire" (adapted from Pasquali, 1998) [26] approved 15 questions for the final composition of the questionnaire for professionals and 22 questions for the patients questionnaire and made suggestions that were considered to improve the intelligibility of issues.

The validated data collection instrument was a semi-structured questionnaire, without respondents' identification, with closed and discursive questions.

The questionnaire for health providers included: (a) Professional training characterization, (b) Drug prescription parameters, bibliographic references, conducting dose adjustment and (c) Service bariatric: prescription dosage forms, specific recommendations for

solid oral dosage form, follow up of patients, knowledge about the therapeutic failure possibility and case reports observed.

The questionnaire for patients included: (a) Socio economic characterization, (b) Pre and post-surgical features: BMI, comorbidities and medications in use and (c) Medication use after bariatric surgery: specific recommendations received and the occurrence of medication intake problems.

The questionnaires were carried out only by a researcher trained and familiar with the instrument.

2.2. Providers

Face-to-face interviews with providers from different specialties regarding the prescription for bariatric patients, with emphasis on prescribing solid oral dosage forms, were carried out. From the list of Medical Professional Registry Council of Maringa, a sample of 10% of the physicians was selected and special attention was given to cover different specialties areas. Medical specialties were chosen as high probability to prescribe for post-bariatric patient. Their graduate medical school, year and specialty of each professional were recorded to show that they did not have the same background (same school, professional experience time and different region of Brazil). The main questions were related to their criteria to prescribe medicines for bariatric patients.

Exclusion Criteria: Providers with less than 2 years of experience and professionals specialized in: urgency, emergency and intensive care unit at hospitals, anesthesiology, dermatology, endoscopy, medical genetics, homeopathy, breast cancer, legal medicine, pathology, pediatrics, radiology and clinical laboratory, were excluded from the protocol, once they rarely prescribed oral medicines for bariatric patients.

2.3. Patients

All patients were seen in the outpatient in 2 different Surgery Centers, Maringa, Parana, Brazil, and their medical records were reviewed retrospectively. A sample of 73 adult patients was randomly selected from a database of all patients who had undergone RYGB between January 1, 2010 and May 31, 2012.

Inclusion criteria: patients older than 18 years old, clinically stable and that had their RYGB bariatric surgery for more than six months up to two years were carried out. The main questions were about their anthropometric data, medicines used before and after 6 months of surgery, if they had health problem and intake of medicines after surgery as tablet or capsules, how they were instructed to swallow the solid oral dosage forms and if they had any problem with these dosage forms.

2.4. Data base search of bioavailability studies with bariatric patients

The following key-words were selected and cross-linked to find articles in the PubMed data-baselines about Bariatric and: pharmacokinetics, absorption, drugs, solid oral tablets; Roux-en-Y gastric bypass and: pharmacokinetics, absorption, drug.

2.5. Statistical Analysis

All statistical analyses were performed using Statdisk Version 11. Summaries of responses and baseline characteristics were expressed as mean and standard deviation and categorical variables as frequency (%) were described. The provider's responses were separated according to years of experience grading less than 10 years of experience as 0 and more than 10 years of experience as 1. The factors considered were: drug absorption is altered in bariatric patient, follow-up of patients, prescribe as first choice tablets for these patients, inefficacy observed and source of information for decision-making (clinical experience or guidelines). Chi-square Tests were applied to measure significance between different factors and variables and the Odds ratio and significance to the level of 0.05 were obtained. For values below 5, we used the Fisher´s exact Test. Identified the significant factor, a logistic

regression was built using Logit method to check the differences in term of years of experience to decision-making for prescribing for bariatric patients.

3. RESULTS

A total of 62 providers completed the survey from 108 providers invited. This sample number represents about 10% of the total number of doctors registered in the Medical Professional Council of Maringa city, Parana State, Brazil. The main demographic characteristics of the providers are presented in the Table 1.

We focused to interview most of infectologists, cardiologists and endocrinologists because the fail in the treatment it is very critical. Most of oncologists refused to participate in the survey. The majority of the providers had more than 10 years of clinical experience (Table 1). In average, they consulted 5 bariatric patients / month. The main topics covered by the questionnaire for providers are presented in the Table 2.

Table 1. Characteristic data of interviewed doctors n=62 (100%)

Gender	**n (%)**
Female	26 (42%)
Male	36 (58%)
State of Medical Graduation	
State	**n (%)**
Parana	30 (48,4%)
São Paulo	12 (19,4%)
Rio de Janeiro	9 (14,5%)
Rio Grande do Sul	5 (8,1%)
Other	6 (9,7%)
Decade of Graduation	
Years	**n (%)**
1970-1979	8 (12,9%)
1980-1989	22 (35,5%)
1990-1999	16 (25,8%)
2000-2009	16 (25,8%)

Medical specialties respondents	**N**
Obstetrics and Gynecology	10
Infectious Diseases	8
Surgery	6
Medical clinic	6
Cardiology	5
Dentistry	5
Endocrinology	4
Psychiatry	3
Gastroenterology	2
Geriatrics and Gerontology	2
Hematology	2
Nephrology	2
Oncology	2
Orthopedics	2
Allergy and Immunology	1
Pneumology	1
Rheumatology	1

Table 2. Clinical and drug prescription parameters answered by the health care providers.

Roux-in-Y gastrectomy interference in the absorption of the medicines:	N (%)
NO	30 (48%)
> 10 years of work experience	23 (37,1%)
< 10 years of work experience	7 (11,3%)
YES	32 (52%)
> 10 years of work experience	20 (32.3%)
< 10 years of work experience	12 (19.4%)
Think patients need specific recommendation for intake tablets and capsules after bariatric surgery:	
NO	30 (48%)
YES	32 (52%)
Recommendation for intake oral forms after bariatric surgery:	
Prescribe liquid forms if it was available or recommend cutting the tablets and open the capsules when it is safe for the patients	20 (32%)
Prescribe tablets and capsules without any special recommendation	42 (68%)
>10 years of work experience	30 (48.6%)
<10 years of work experience	12(19.4%)
Inefficacy with oral medicines:	
Have never experienced any lack of effect of medicines prescribed	28 (45%)
Alleged that some patient had problems but they were not sure it was because the medicine absorption	24(39%)
Have observed treatment failure and attributed it to the drug absorption failure after bariatric surgery	10 (16%)
Doses adjustment:	
Just followed instructions from the labels and do not do any adjustment if it is not written	39 (62.9%)
Adjusted the doses based on: their kidney function	10 (16.13%)
their weight	8 (12.9%)
Others	5 (8.07%)
Follow up the patients symptoms:	
YES: Monitoring for chronic treatment	22 (35.4%)
Consultations Return doctor	20 (32.3%)
NO: The consultations were occasional	20 (32.3%)
Factors influencing the prescription:	
Efficacy	41 (56%)
Adherence to treatment	20 (28%)
Individual needs	12 (16%)
Prescribing support used	
International Guidelines, Scientific Journals, textbooks	36 (58%)
Clinical experience	26 (42%)

Grouping the providers with more than 10 years and less than 10 years of clinical experience and comparing their answers about bariatric patients, 51.6% of all providers

believe that bariatric surgery may compromise the absorption of drugs and only 19.5% of young providers believe this may happen.

The only significant differences between young and older providers were related to their decision to recommend other oral dosage forms than tablets and the following up the patients. Comparing the results of Chi-square and Fisher exact test of young and old providers, the older providers are more likely to follow up the patients and recommend tablets as first choice ($p=0.037$). The factors that drug absorption is altered in bariatric patients, follow up the patients, source of information they use and inefficacy observed were not significant different between young and old providers, but when grouped them with prescription of tablets as first choice for bariatric patients and follow up, a significant differences were found in the binary logistic regression ($p=0.014$) and improvement in the correlation was seen. The statistical analyses are presented in the Table 3. The older providers were 3.85 (1/0.26) times more likely to follow up the patients and 5.88 (1/0.17) times more likely to prescribe tablets without any recommendation as breaking or open the capsules for bariatric patients than the young providers.

The number of providers who have inefficacy and confirmed that it was because absorption was 16% of total providers, 55% of them have seen inefficacy, but they could not say if it was because absorption problem. Their decision for prescribing medicines followed the international guidelines (58%) or their clinical experience (42%), but in the guidelines they do not describe any adjustments because the gastrectomy and obesity. 62.9% of the providers just followed instructions from the labels and did not do any adjustment if it was not written and who adjusted the doses they based mainly on their kidney function (16.13%), weight (12.9%) or on other clinical and laboratory findings, such as signs and symptoms, blood glucose, triglycerides, cholesterolemia, hormones (8.07%).

Table 3. Statistical Analysis of clinical parameters followed by health care providers.

Event: Year of experience (young and old providers)		
Factors	**Chi-square P**	**Fisher Exact Test P**
Absorption affected	0.188	0.249
Follow up	0.084	0.120
Prescription of tablets as first choice	0.037	0.065
Inefficacy observed	0.586	0.716
Number of patients/months	0.473	0.56
Source of information	0.778	1.0

Logistic Regression Analyses – Binary

Predictor	**Coeficient**	**P**	**Odds ratio**	**95% CI** Lower	Upper
Constant	0.2089	0.703			
Follow up	-1.330	0.043	0.26	0.07	0.96
Tablets as first choice	-1.781	0.038	0.17	0.03	0.91

In general, the non-bariatric doctors had observed very few problems with medicines in bariatric patients and the majority of providers do not change their routine for decision-making just because the patients had gastrectomy surgery. Most of them believe it may affect the absorption of the medicines, but they just followed the standard prescription based on the guidelines or clinical experience with non-bariatric patients.

Seventy three patients answered the survey. The main demographic characteristics of the patients are presented in the Table 4. Evaluating the results, only 24 patients presented some health problems not related to the surgery during the period of study. Twenty of them were taking tablets, 1, syrup and 1 parenteral. Before the surgery, the patients were taking in average 2.8 ± 1.3 tablets of different composition, including the polivitamins supplements and after 6 months of surgery they had reduced to 2.5 ± 1.2. Fifteen patients were informed by the providers how to take medicines regarding the time and standard doses, before or after the meals. Five patients did not receive any instructions. Eleven patients reported having problems related to the surgery like anastomotic stricture or staple line leak, bowel obstruction, marginal ulceration or fistula formation.

Table 4. Distribution of patients according to the socioeconomic and pre/post-surgery

variables.

Socioeconomic variables	
Gender *(female)*	58 (79%)
Age *(years)*	37.9 ± 10.6
Pre and post-surgery variables	
Time post-surgery *(months)*	13.2 ± 6.4
BMI *(kg/m^2)*	
Pre-surgery	41.3 ± 4.3
Post-surgery	27.2 ± 3.9*
Medications *(average/patient*)	
Before	2.8 ± 1.3
After surgery	2.5 ± 1.2
Comorbidities *(average/patient*)	
Before	4.4 ± 1.9
After surgery	2.4 ± 1.4
Physical activity after surgery *(non-practicing)*	29 (39.8%)
Nutritional guidance after surgery *(patients with partial follow-up)*	51 (69.9%)
Smoking after surgery *(non-smokers)*	62 (84.9%)
Use of alcohol after surgery *(users)*	38 (52.1%)

Ten patients stopped taking all medication after surgery, 26 decreased at least one drug, 7 did not take before and among them 4 began to take nutritional support, 19 remained with the same amount of medicines. The overview of medicine intake and problems related to the patients interviewed are listed in Table 5.

Table 5. Overview of medicine intake and medication use after surgery by patients.

Patients interviewed	73 (100%)
Medication use after bariatric surgery:	
Remained with the same amount of medicines	19 (26%)
Decreased at least 1 medicine	26 (35.7%)
Stopped taking medicines	10 (13.7%)
Did not take any medicine before the surgery and started nutritional support	4 (5.5%)
Advised to avoid some medicines and take care of medication after the procedure	5 (6.8%)
Health problems after surgery:	
Presented health problems related to the surgery	11 (15.1%)
Presented health problems not related to the surgery	25 (34.2%)
Tablets was recommended	20/25 (27.4%)
Recommendation of standard dosage regimen (doses and dosing interval)	15/25 (20.5%)
Did not get any recommendation	5/25 (6.8%)

According to the patients who need a prescription, 22 received tablets representing approximately 90%. Among the main problems related by the patients were: dumping problems (34 patients), abdominal pain because non-steroid antiinflamatory drugs (6 patients), difficult of swallow because the size of the tablets (4 patients), urinary tract recurrent infection (2 patients), heartburn (2 patients), reduced effect of levothyroxine (1 patient) and over effect of acetaminophen (1 patient). Only for polivitamins, the bariatric surgeons recommended to cut the tablets. Some patients unofficially reported they cut or crush the tablets on their own, without proper counseling, due to the large size of the tablets and swallowing difficulty, and because of this may have been an underestimation of the percentage of patients who reported such difficulties.

Searching for literature to support the providers' decision-making and among all journals they cited, the journals of American Thoracic Society Journals presented the highest number of articles related to bariatric surgery (68 articles) followed by The New England Journal of Medicine (58 articles). However, only 3 of them showed articles related to bsorption rate of medicines and the number of journals with data of pharmacokinetics studies were small: only case-reports or small number of patients and also information about RYGB were reported (Table 6). Most of articles related to pharmacokinetics studies in bariatric patients were published in journals not cited by the providers (Table 7).

We also searched in the clinical trials website (Avaiable on: http://goo.gl/FbfeFp [45]) about the pharmacokinetics studies in bariatric patients and when the key-words were used: bariatric surgery, pharmacokinetics and absorption, only 8 studies were listed, which address the following drugs: Fondaparinux, Sertraline, Moxifloxacin, Vitamin D-Cholecalciferol, Morphine and Metformine.

Table 6. Scientific literature used by healthcare providers for decision-making about drug prescription for bariatric patients.

Journals cited by the providers	**No. of citation [1]**	**No. of Bariatric articles [2]**	**No. of Pharmacokinetic articles [3]**
American Thoracic Society Journals	1	68	0
New England Journal of Medicine	6	58	0
The Journal of Clinical Endocrinology & Metabolism	2	58	0
Endocrine Reviews	1	52	0
Diabetes Care	1	30	1
Arquivos Brasileiros de Cirurgia Digestiva	1	24	0
Medical Clinics of North American Journal	1	24	0
British Medical Journal	1	16	0
Arquivos Brasileiros de Endocrinologia e Metabologia	3	13	0
Neurology	1	8	0
Arquivos Brasileiros de Gastroenterologia	1	6	0
Journal of Antimicrobial Chemotherapy	1	4	4
Arquivos Brasileiros de Cardiologia	2	3	0
Arquivos de Neuro-psiquiatria	1	2	0
Journal of Oral and Maxillofacial Surgery	1	2	0
Journal of Clinical Periodontology	1	2	0
Clinics in Chest Medicine	1	1	0
Antimicrobial Agents and Chemotherapy	1	1	1
Revista Brasileira de Psiquiatria	1	1	0
Clinical Infectious Diseases	4	0	0
Infection Control and Hospital Epidemiology	1	0	0
Journal of Infectious Disease	1	0	0
Journal of Endovascular Therapy	1	0	0

[1]Number of times it was cited by the providers. [2]Number of articles related to bariatric patients. [3] Number of articles related to bariatric patients and pharmacokinetic/bioavailability/drug disposition

Table 7. Journals with pharmacokinetic studies with RYGB bariatric patients.

Drugs	Journals	Bioavailability (N=patients)
	Clinical Journals	
Calcium citrate	Surgery for Obesity and Related Diseases (2013)	Effervecent potassium calcium citrate has superior biavailability (N=15)
Calcium citrate and calcium carbonate	Obesity Surgery (2009)	Calcium citrate has superior bioavailability (N=18)
Levothyroxine	Thyroid (2013)	Unaltered (N=7)
Levothyroxine	Obesity Surgery (2013)	Oral liquid has superior bioavailability (N=4)
Metformine	Diabetes Care (2011)	Increased (N=12)
Serotonin reuptake inhibitors (SRI)	The American Journal of Psychiatry (2012)	Decreased (N=12)
Sertraline	Surgery for Obesity and Related Diseases (2012)	Decreased (N=5)
Temozolomide	Journal of Neuro-oncology (2009)	Unaltered (N=1)
	Pharmaceutical Journals	
Acetaminophen	Clinical Pharmacology and Therapeutics (2011)	Increased (N=12)
Amoxicillin	Clinical Pharmacology and Therapeutics (2011)	Decreased (N=12)
Atorvastatine	Clinical Pharmacology & Therapeutics (CPT) (2009)	Variable (N=12)
Azithromycin	Journal of Antimicrobial Chemotherapy (2012)	Decreased (N=14)
Cyclosporine	Clinical Pharmacology & Therapeutics (CPT) (2009)	Decreased (N=12)
Duloxetine	Journal of Clinical Psychopharmacology (2013)	Decreased (N=10)
Erythromycin	Journal of Clinical Pharmacology (1984)	Decreased (N=1)
Ethanol	British Journal of Clinical Pharmacology (2002)	Increased (N=12)
Linezolid	Journal of Antimicrobial Chemotherapy (2013)	Unaltered (N=5)
Moxifloxacin	Journal of Antimicrobial Chemotherapy (2012)	Unaltered (N=12)
Talinolol	Talinolol	Decreased (N=12)

The search covered from 2002 to September, 2013 for RYGB and JIB.

4. DISCUSSION AND CONCLUSION

4.1. Discussion

The number of reports showing how to manage a bariatric patient and the quantity of information about drug bioavailability had not increased in the same proportion of the number of bariatric surgery in the last 10 years. According to the literature, this is the first study on pharmacotherapeutic management after bariatric surgery involving non bariatric health providers.

In order to avoid providers with the same background (same graduation year, school, specialty, region or gender) we interviewed providers with highest probability to prescribe oral dosage forms according to their consent to answer the survey.

Our study showed that the vast majority of interviewed providers do not change the prescription of solid oral medicines because the gastrectomy. The source of information they use do not supply enough clues for safely prescribe oral dosage forms for bariatric patients.

The literature brings scarce information about the bioavailability of drugs and depending on the medicines, they observed increased effect [7,13,27,40], reduced effect [13,27,33,34,39], no alteration effects [13,30,35,42,43].

Several articles recognize the lack of information on absorption problems, but they recommend some care to prescribe the medicines for this population [4,5,12,13,46] and these information are not reaching the providers.

According to our study, most of providers have not paid attention to the absorption problem of tablets and they prescribed medicines without giving any recommendation about how to swallow tablets or changing for oral solution or suspension, if they were available.

The majority of young providers they changed the tablets for other formulation, but at same time, they did not follow up the patients to see if the patients had problems or not. On the opposite side, the older providers prescribe tablets but they follow up the patients more than the younger ones.

According to the patient responses, 90% received tablets, only 2 patients received a prescription with oral solution and also their formulation was changed because they complained they could not swallow the tablets. This was observed in the follow up consulting, meaning that the providers had prescribed tablets in the first consulting.

Other patients related that they decided to cut or open the capsules without saying to their providers and they did not observe any problem of efficacy after that. Recommendation for cutting or open the capsules and drink with fractionated small amount of water are published in some articles [4,5]. Other recommendations are also available, such as giving preference to liquid or chewable formulation [47].

Inefficacy of the medicines was observed in 55% by the providers, but not all reported the inefficacy was due to absorption problems. Most of related inefficacy was due to the difficult to swallow the tablets and they had to change the formulation, so the providers (39%) could not say if it was due absorption problem or the patients were not taking the medicines properly. This happened most frequent with non-steroidal anti-inflammatory drugs, which tablets are big and they could not swallow them.

Precautions for prescribing tablets of non-steroidal anti-inflammatory drugs for bariatric patients have been reported because they may provoke marginal ulcer and gastric bleeding [48].

Inefficacy was observed for medicines like analgesics and contraceptives and there were recommendation to change the analgesic to liquid formulation and to use an additional contraceptive method, or substitute for other devices, transdermal patches or vaginal rings [4,5]. In our study, reduced effects of levothyroxine and urinary tract antibiotics were observed in one patient and commented by the providers.

The target population included in this study was patients clinically stable after 6 month of the surgery up to 2 years after surgery who underwent RYGB surgery. Most of them lost

considerable weight and the dosage of medicines for chronic diseases they were taken before should be adjusted to normal weight doses. This could be seen by the study carried out by Hamilton et al (2013) with pharmacokinetics studies of Linezolid tablets and intravenous infusion, which higher concentration was observed in patients after the surgery, because the total body weight had reduced compared to concentration before the surgery [42].

Clinics and hospitals where pharmacists are not engaged in the patient care, the bariatric patients may not be properly assisted and furthermore the vast majority of providers are focused on pharmacodynamics and less on pharmacokinetics, so because pharmacokinetics studies absorption, distribution, metabolism and excretion of drugs, which are important parameters for doses adjustment for physiological or pathological changes in the body. This may be the reason that most of providers just followed the guidelines for drug prescription and did not do any formulation adjustment.

Futhermore, the guidelines, in general, do not describe any recommendation for bariatric patients and even for obese patients [1]. Only in the last updated of Clinical Practice Guideline of the American Association of Clinical Endocrinologists and other organizations, a small note was added about the use of medications: to avoid nonsteroidal antiinflammatory drugs and immediate-release preparations are preferable to extend release or enteric-coated preparations [47].

An important gap for a good drug prescription for bariatric patients is that information about pharmacokinetics studies are published in pharmaceutical journals than the clinical journals and the main recommendation for adjusting the dosage forms are not reaching the providers.

Also, the lack of studies about drug absorption problems compared to nutritional, psychological and physical condition studies are because the regulation to perform bariatric surgeries requires a minimum staffs with a surgeon, nurse, psychologist, nutritionist and

physical educator, but not a pharmacist and this may be one of the reason there are very few articles related to medicines in bariatric patients compared to articles of hypovitaminosis [47,49], bone problems [50,51], psychiatric consumption of drugs [52-54] and outcomes from the surgeries [55-64].

The lack of vitamin and minerals appears slowly [47] and can be treated quickly as out-patient, but a lack of effect of medicines, like for sepsis, hypertension or diabetes, leads the patients to critical health conditions which most of time we cannot treat as out-patient and needs hospitalization. Furthermore, the providers will consider as a resistant microorganisms or resistant hypertension or diabetes.

The main pharmaceutical recommendation for drug prescription and drug administration to support decision-making of providers is summarizing in the Table 8. In general, an important consideration on management of patients following bariatric surgery is a patient-specific nutritional and pharmacotherapeutic monitoring plan, which is crucial to minimize adverse events and maximize therapeutic outcomes.

Table 8. Main Pharmaceutical Recommendations for Prescription of Medicines for Bariatric Patients.

Main Pharmaceutical Recommendations
Dosage forms Recommendations
1) Palatability and convenience may play an important role in patient adherence and should be considered; [65]
2) The formulations should be changed to a liquid medication formulation because it could increase absorption by eliminating the need for drug dissolution; [4, 5, 46, 47, 66, 67]
3) Should be changed the extended-release, delayed-release and enteric- or film-coated product formulations, to avoid potential decreased bioavailability and prolonged dissolution of the former; [6, 46, 65, 66]
4) Crushable, chewable or immediate-release dosage forms should also be used because they may improve bioavailability post-surgery; [6, 65, 68, 69]
5) Tablets may be swallowed whole if they are no larger than the diameter of a pencil eraser; [66, 67]
6) Consider other administration approaches, including subcutaneous, intravenous, rectal, vaginal, intranasal, and transdermal routes if available; [5]
7) Suppositories should be avoided in case the patient develops diarrhea or dumping syndrome.[65]
Some Specific Drug Classes Recommendations

1) Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and antiplatelet agents should be avoided because the risk or GI bleeding and marginal ulceration; [70]
2) The overall absorption of some hormonal contraceptives is altered. The efficacy of depot medroxyprogesterone acetate and combination contraceptive vaginal ring may be the preferred contraceptive agents for women following bariatric surgery; [71, 72, 73]
3) Substances that depend on acidic environment are optimally soluble within an acidic environment and the co-administration of ascorbic acid. Calcium carbonate should be changed to calcium citrate to improve absorption; [28, 65]
4) Tablets of bisphosphonate used after RYGB may develop marginal ulceration and gastroesophageal injuries and intravenous bisphosphonate therapy should be a safer choice. [74,75]

There were some limitations to this study. We could not find a high number of patients with health problems, maybe because the short of period time after the surgery they were selected, so studies with patients after 5 to 10 years of surgery should be carried out.

4.2. Conclusion

Our study shows for the first time how bariatric patients have been managed by the non-surgeons and they have been treated as normal patients. The old providers prescribes more tablets but they do follow up more frequent than the young providers, while young providers prescribe different dosage forms, but they do not follow up the patients. The intervention of the pharmacist to help the management of drugs for this population would reduce therapeutic failures.

While we do not have precise information about drug availability in bariatric patients, useful precautions should be followed, like given liquid formulation or if it is not available, changing for chewing formulation, breaking when the tablets are not coated for stability purposes.

4.3. Practice Implications

As most of the providers included in this study did not attempt about the importance of the stomach and duodenum for drug prescription, this may represent a high risk for these population, once the failure or over dosage of the medicines may aggravate their disease.

Conflict of interest statement

None of the authors have conflicts of interest or additional financial disclosures to report.

Disclousure

We confirm that all patient/personal identifiers have been removed or disguised so that patient/person(s) described are not identifiable and cannot be identified though the details of the history.

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Artigo 2: “Short communication: Some evidences that bioavailability of some highly soluble drugs are unaltered in Roux-en-Y bariatric patients.”

Short Communication: Some evidences that bioavailability of some highly soluble drugs are unaltered in Roux-en-Y bariatric patients.

Bárbara Letícia da Silva Guedes[1], Maiara Camotti Montanha[2], Sergio Seiji Yamada[3], Sandra Regina Bin Silva[3], Daoud Nasser[4], Elza Kimura[5].

Abstract

Background
Patients undergone Roux-en-Y Gastric Bypass at some stage will need to intake oral antimicrobial and antihypertensive drugs as tablets or capsules and it is a big concern, since the gastric environment is changed and the rate of disintegration, dissolution and absorption of the drugs may be altered in these patients affecting the drugs bioavailability.

Objective
To investigate the dissolution rate of drugs from different Biopharmaceutical Classification System (BCS) in a modified gastric environment simulating the stomach of patients undergone RYGB surgery and compare their dissolution rate with the bioavailability studies using the BCS this was carried out.

Methods
An *in vitro* dissolution model with low volume (50 ml), low acid strength (water or HCl 0.01N) and low motility (10 rpm) was used. Commercially drug formulations available exclusively in immediately release tablets and capsules were chosen to carried out the test: Antibacterials: Ciprofloxacin, Doxycycline, Metronidazole and Sulfadiazine; Antivirals: Atazanavir, Lamivudine, Stavudine and Zidovudine, and Antihypertensives: Atenolol, Captopril, Propranolol, Furosemide, Hydrochlorothiazide.

Results
High solubility drugs class I and III drugs had a slight delayed in the dissolution time and most of them achieved the dissolution percentage prolonging the time for less than double time in small volume medium, low acid strength and low of motility. On the other side, the low solubility drugs class II and IV presented dissolution time higher than double of the time. The time required to class I and III to dissolve were 1.5 ± 0.5 times while class II and IV were 3.83 ± 1.17 times. Comparing the bioavailability studies of drugs class I and III, most of them were unaltered, while class II or IV were decreased.

Conclusion
It would be expected that most of the tested drugs, specially BCS class I and III, will not present bioavailability problems in bariatric patients, but special attention should be pay for low soluble drugs: Ciprofloxacin, Sulfadiazine, Atazanavir, Hydrochlorothiazide and Furosemide, which may present a delay or reduction in the onset of therapeutic effects of drugs.

Keywords: bariatric surgery, pharmacotherapy, prescription, bioavailability, pharmacokinetics.

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[1] Post-Graduate Program in Bioscience and Physiopathology. State University of Maringa, Parana, Brazil.
[2] Undergraduate degree in Pharmacy. Pharmacy Department. State University of Maringa, Parana, Brazil.
[3] Regional University Hospital of Maringa. Clinical Research and Bioequivalence Nucleus, Maringa, PR, Brazil.
[4] Regional University Hospital of Maringa, Parana, Brazil.
[5] Pharmacy Department. Post-Graduate Program in Bioscience and Physiopathology. Clinical Research and Bioequivalence Nucleus, Maringa, Parana, Brazil.

Adress for correspondence: Prof.ªDr.ª Elza Kimura Grimshaw. Hospital Universitário Regional de Maringá, Núcleo de Pesquisa Clínica e Bioequivalência. Avenida Mandacarú, 1590, CEP: 87083-240, Maringa, Parana, Brazil. Telefone: 55 44 3011 9202
Email: elzakimura1@gmail.com

INTRODUCTION

Concerns about prescription of medicines for patients undergone bariatric surgery has increased in recent years. Only in 2010 about 60,000 surgical procedures were carried out [1,2] in Brazil and the main reason for this concern is that most of the type of surgery that has been carried out was the Roux-en-Y Gastric Bypass (RYGB), representing more than 75% of the total of surgeries. The partial removal of the stomach and duodenum-jejunum bypass surgery in RYGB leads to limitation in digestive capacity, decrease the absorption site, modifies the gastric pH, reduced or total absence of gastric transit [3] and most of these patients present nutritional deficiency after the procedure an a need for nutritional counseling is required [4].

The same factors that interfere with nutrient absorption can also affect the absorption of drugs and despite of bariatric procedures have been done for more than 10 years, few studies on the influence of drug absorption were investigated. Furthermore, the majority of published studies involved patients who had undergone Biliopancreatic Diversion (BPD) or Jejunoileal Bypass (JIB) and these procedures involving anatomical changes drastically different from RYGB [3]. Some reviews have been carried out on precautions for drug administration; however, data showing the change in bioavailability of oral drugs are scarce[5,6].

Oral intake of antimicrobials as tablets or capsules is extensively used and for patients undergone RYGB is a big concern, since the gastric environment is changed and may have affected the rate of absorption of the antimicrobials. As antimicrobials represent a class which oral bioavailability impairment is critical for the patients, once sub-therapeutic levels may aggravate their clinical condition and induce microbial resistance leading to sepsis[7,8]. Studies on oral administration of this drug class in bariatric patients should be deeply investigated. On

the same way, the antihypertensive medicines are other class of big concern for bariatric patients because the high risk of comorbidities [4].

Mathematical modeling and mechanistic approaches [9] has been proposed for mimicking the behavior of medicines in the gastric environment after oral administration, but no test, even *in vitro* dissolution test were carried out to check the dissolution of antimicrobial and antihypertensive solid oral dosage forms in low volume and slow motility.

Drugs which are highly soluble and high permeable are exempt of bioequivalence studies because they are expected to dissolve in the gastrointestinal (GI) environment and according to FDA guidelines and Biopharmaceutical Classification System (BCS) [11], drugs which are highly soluble and high permeable - BCS class I - are only likely to be dependent on drug dissolution and GI emptying time. The other BCS classes are: class II (low solubility and high permeability), class III (high solubility and low permeability) and class IV (low solubility and low permeability). So, the *in vitro* dissolution profile of some drugs is important to establish *in vivo* correlations, but we need to know which variables may influence drug release [10,11].

According to BCS class I, as the drugs may be exempt of bioequivalence studies, they may not cause bioavailability problems in a modified environment like RYGB even for tablets with high content of active substances and it is more likely that class II or class IV medicines will not dissolve completely in this modified gastric environment[10,11].

So, our study aimed to investigate which BCS class of medicines may present problems in most bariatric patients undergone RYGB surgeries and to compare the dissolution rate of the medicines in a modified environment of bariatric patients, with low volume, low acid strength and low motility classifying them according to BCS.

MATERIALS AND METHODS

Search for commercially available drug dosage forms of antibacterials, antivirals and antihypertensives exclusively in capsules or tablets: In order to define which antimicrobials and antihypertensive medicines we should test for simulation of RYGB environment, a search of commercially drug formulations available exclusively in immediately release tablets and capsules were carried out. Solid oral dosage forms were searched in the websites of Food and Drug Administration (FDA)[12], European Medicine Agency (EMA)[13] and Brazilian Health Surveillance Agency (ANVISA)[14] of registered medicines. Drugs that were available as liquid forms, like oral solution / suspension, injectable forms or drug association were excluded.

Modified Dissolution Test

Drugs: The antibacterials: Ciprofloxacin (Prati-Donaduzzi), Doxycycline (Sandoz/Novartis), Metronidazole (NeoQuímica) and Sulfadiazine (Sobral); Antivirals: Stavudine (LAFEPE), Zidovudine (Farmanguinhos), Lamivudine (Farmanguinhos), Atazanavir (Bristol-Myers Squibb) and Anti-hypertensive drugs: Propranolol (EMS), Atenolol (Prati-Donaduzzi), Furosemide (Teuto/Pfizer), Captopril (Teuto/Pfizer) and Hydrochlorothiazide (Germed/EMS) were purchased by the University Hospital and kindly supplied to carry out the studies. The antivirals were supplied from the HIV Disease Control Health Center of Maringa city.

The BCS was searched for each drug supported by World Health Organization (WHO) guidance of biowaiver[15]. Additional source used was Therapeutic System Research Laboratories (TSRL, Inc., Ann Arbor, MI) directed by Amidon[16]. The drugs were classified according to the BCS in: Class I = Doxycycline, Metronidazole, Propranolol, Stavudine and

Zidovudine; Class II = Atazanavir; Class III = Atenolol, Captopril, Hydrochlorothiazide and Lamivudine; Class IV = Ciprofloxacin, Furosemide and Sulfadiazine.

Standards Preparation and working solutions: The average weight of 10 tablets or capsules of each drug was measured and they were pulverized using mortar and pestle. Approximately 200 mg of each drug was weighted and diluted to final concentration of 50 mg/L in 0.01N HCl or distilled water, according to dissolution tests described in the US Pharmacopoeia 33ed. Atazanavir, Ciprofloxacin, Doxycycline, Metronidazole, Sulfadiazine, Captopril, Hydrochlorothiazide, Atenolol, Furosemide and Propranolol were diluted in 0.01N HCl, while Stavudine, Lamivudine and Zidovudine were diluted in distilled water. The solutions were measured according to maximum absorption of each drug using a spectrophotometer Shimadzu UV-Mini, Japan. The assays were carried out in triplicate for each drug and the maximum absorption measured were considered as 100% content of each drug in order to compare to dissolution profile of each tablet or capsule.

Simulated dissolution test of gastric environment of bariatric patient: To simulate the gastric volume, acid strength and motility, the volume of the fluid, the pH and the speed of rotation were reduced and the tests were performed in the Dissolution apparatus (ERWEKA model DT 800 Low Head, Heusenstamm, Germany) according to the following condition: six tablets or capsules of each drug were put in the apparatus 1 (basket), in a volume of 50 ml of 0.01N HCl (Atazanavir, Ciprofloxacin, Doxycycline, Metronidazole, Sulfadiazine, Captopril, Hydrochlorothiazide, Atenolol, Furosemide and Propranolol) or 50 mL of water (Stavudine, Lamivudine and Zidovudine) and 10 rpm in a conical tube of 100 mL with rounded bottom simulated the USP official apparatus incubated in a water bath at 37°C. The sampling times were carried out at 10, 20, 30, 60 minutes and extended up to two hours for drugs that did not achieved the USP 33ed requirements for dissolution test. The drug absorptions of each

sampling time were measured in spectrophotometer and their drug contents were calculated compared to their respectively standard solutions.

Statistical Analysis

The descriptive analyses were carried out using SAS® version 8.2. The mean (M) and standard deviation (SD) and 95% confidence interval (CI) were used to compare the time for accepted dissolution percentage, considering 1 as regular time, double time = 2, three times = 3, four times = 4 and more than 4 = 5 with BCS class I and Class II or IV, were calculated. Also the amount of active substance with the dissolution time was calculated.

RESULTS

We chose 4 antibiotics from different classes, 4 antivirals and 5 antihypertensive drugs to investigate the dissolution rate in a modified environment. The choice was also based in the BCS classification to compare the drug dissolution rate among the classes.

The antivirals Ritonavir and Lopinavir tablets were excluded from our study because they needed bile salts or emulsifiers to dissolve it. Other antimicrobial drugs were available in liquid oral dosage forms and they should be the first choice to treat bariatric patients with infection. The Figure 1 shows the dissolution profile of the drugs in the modified gastric environment and the Table 1 shows the percentage of the drugs dissolved on the limit time required by the FDA.

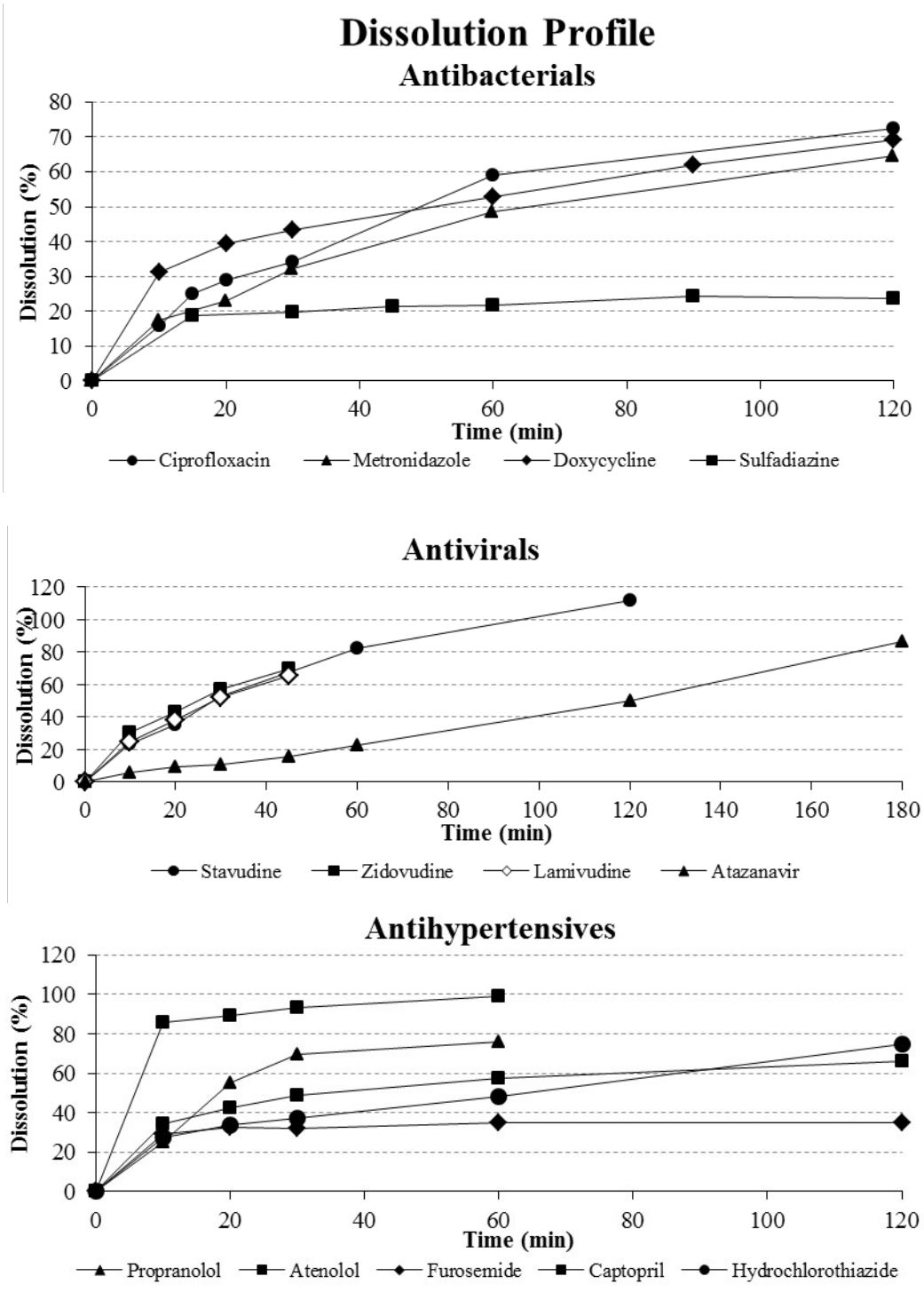

Figure 1. Dissolution rate of the drugs in bariatric RYGB simulated gastric environment.

Table 1. Dissolution percentage of the drugs classified according to BCS.

Drug	Therapeutic class	% Dissolved	Tolerability	Time (minutes)
		BCS Class I		
Doxycycline	Antibacterials	61.81±5.71	≥ 85%	60
Metronidazole		48.65±12.16	≥ 85%	90
Propranolol	Antihypertensive	69.73±3.67	≥ 75%	30
Stavudine	Antivirals	53.07±7.83	≥ 80%	30
Zidovudine		69.57±10.27	≥ 75%	45
		BCS Class II		
Atazanavir	Antiviral	15.83±2.24	≥ 75%	45
		BCS Class III		
Atenolol	Antihypertensives	48.65±7.15	≥ 80%	30
Captopril		89.39±5.53*	≥ 80%	20
Ciprofloxacin	Antibacterial	34.17±7.82	≥ 80%	30
Hydrochlorothiazide	Antihypertensive	48.21±4.3	≥ 60%	60
Lamivudine	Antiviral	65.27±6.08	≥ 75%	45
		BCS Class IV		
Sulfadiazine	Antibacterial	24.24±3.29	≥ 70%	90
Furosemide	Antihypertensive	35.01±4.83	≥ 60%	60

The results of the dissolution profile of the tablets and capsules among all tablets and capsules tested showed that only Captopril (89.39 ± 5.53%) passed the FDA requirements in the regular time. Among the antibacterials, extending the time for dissolution (Figure 1), Doxycycline and Metronidazole almost reached the required % dissolved in less than double the time, but Ciprofloxacin took 4 times more to dissolve and Sulfadizine did not dissolved even prolonging the time for 2 hours.

The antivirals Stavudine, Zidovudine and Lamivudine required a little more time to pass the test and it is expected they will not present absorption problems in bariatric patients, since they are highly soluble. Atazanavir required 3 times more the tolerance time to dissolve.

The antihypertensives Propranolol needed a slight longer time to dissolve, but less than double time, Hydrochlorothiazide needed twice the time to achieve the tolerance % of dissolution, but a big concern was Furosemide that dissolved less than half dose after prolonging contact time for 2 hours.

Atenolol, a class III drug was expected to dissolve faster than the other, but surprisingly, it took more than 4 times of the regular time to dissolve.

The time required for BCS class I and III drugs (1.5 ± 0.5h; 95% CI from 1.038 to 1.962) to dissolve the tablets were significant faster than the BCS class II and IV (3.83±1.17h; 95% CI from 2.606 to 5.060). The 95% CI for the mean difference between the high soluble drugs compared to low drugs were -3.286 and - 1.214, respectively, with t-student test significant p=0.003.

Comparing the amount of active ingredient in each of the tablets or capsules, no correlation was found between the amount of active substance or size of the tablets and the dissolution rate (p=0.250).

Pharmacokinetics drug data in bariatric patients and BCS Classification

A search of antibacterial, antiviral and antihypertensive drugs from literature exploring the key-words of pharmacokinetics, bioavailability and absorption following RYGB were carried out. Only 11 drugs pharmacokinetics studies were found in patients undergone RYGB (Table 2).

Table 2. Antibacterial, Antiviral and Antihypertensive drugs Bioavailability Studies following RYGB bariatric patients

Drugs	SCB class	Drug Bioavailability	Therapeutic class
Amoxicillin [17,18]	IV	Decreased	Antibacterials
Ampicillin [19]	-	Decreased	
Azithromycin [20]	II	Decreased	
Duloxetine [21]	II	Decreased	
Erythromicin [29]	II	Unaltered	
Linezolid [30]	I	Unaltered	
Moxifloxacin [31]	I	Unaltered	
Nitrofurantoin [17]	IV	Decreased	
Lopinavir [33]/ Ritonavir[33]	IV or II / IV	Increased	Antivirals
Talinolol [18]	II	Decreased	Antihypertensive

The only two class II drugs studied showed that dissolution were unaltered, while most of class II and IV had decreased bioavailability.

DISCUSSION

The results from this study presents a comparison of the dissolution profile of different BCS drugs as intact tablets or capsules. Most of BCS class I drugs presented reasonable dissolution rate in small volume medium, low acid strength and low of motility.

Our study differs from Darwich et al. (2012) because most of patients described in their study they had switched to liquid formulation, chewable tablets or crushed tablets, and the drug release and absorption would not be delayed by the disintegration and dissolution process. Once the tablets are crushed, the superficial area and the wettability of the powders increase and improve the dissolution rate. Also, the movement of the particles from the small pouch of the stomach to jejune will be faster than the intact tablet. Once the drugs are in the jejunum, the absorption will follow as non-bariatric patients', where the drug permeability will be essential for the absorption, because these patients had intact jejune and had bypassed

only the stomach and duodenum. This may be one of the reasons why they could not find significant absorption difference between high and low soluble drugs.

The BCS classification is been used as an important tool to biowaiver the bioequivalence studies and the dissolution test could replace the bioavailability studies. Although the clinical performance of the majority of approved immediate release oral drug products can be assured with *in vitro* dissolution test, we do not discard the necessity to confirm the "in vitro" results in bariatric patients undergone RYGB.

The drug prescription in the study described by Darwich et al (2012) were from bariatric surgeon and they recommended crushing or changing to liquid formulation, but according to our previous study interviewing non-bariatric health providers, most of them do not give any instructions about crushing or changing to liquid formulation and the patients swallow the tablets as it is. In spite of lack literature to support our hypothesis that there is a correlation between BCS class drugs of high solubility (I and III) and low solubility (II or IV) medicines and the dissolution rate, we can see that most of class I drugs bioavailability results were unaltered, while the class II or IV had decreased levels.

According to most common problems reported by the patients about the medicines, the common complaint was because they could not swallow the medicines because the size, the tablets/capsules were stacked in the stomach, stomachache and abdominal discomfort suggesting that the amount of active substance and excipients were influencing the dissolution of the tablets or capsules, but when the dissolution time were correlated with the total weight of the tablets, a poor correlation was found.

The low rotational speed, low volume and low acid strength used in the dissolution test may have interfered with the dissolution rate of some coated tablets like Ciprofloxacin and Lamivudine, but this condition will be find in the bariatric patient´s stomach.

Ciprofloxacin need low pH to dissolve the coating layer and this maybe the reason Ciprofloxacin dissolution rate was delayed.

None bioavailability problems with class I drugs were found in the literature and also in our previous study interviewing patients. On the other side, most of bioavailability problems were related to class II and IV drugs and this was confirmed in our study. The medicines with unaltered bioavailability are all highly soluble drugs, while the drugs with altered bioavailability belonged to other BCS classes, II or IV.

According to our results, seems that the absorption of the drugs in RYGB patients are dependent on the dissolution and solubility of the drugs, while permeability through the membranes will take place only after the drugs were dissolved and reached the jejune, showing that there is evidence that the BCS class of medicines may play role in the absorption of tablets in bariatric patients after comparing the literature data with the results found in our modified dissolution test. So, it is expected that most of the drugs, specially BCS class I and III, will not present bioavailability problems in bariatric patients because the dissolution process, but special attention should be paid for Ciprofloxacin, Sulfadiazine, Atazanavir, Atenolol, Hydrochlorothiazide and Furosemide, which may present a delay or reduction in the onset of therapeutic effects of drugs.

Prescription of low solubility drugs should be changed to liquid formulation and avoided or a strict follow up of patients should be carried out, once the medicines tested in this study may present therapeutic failure and increase the risk of mortality.

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CAPÍTULO III

CONCLUSÕES

É possível fazer as seguintes observações finais a partir do estudo do manejo e prescrição farmacoterapêuticos e da simulação de dissolução de formas farmacêuticas orais em pacientes submetidos à cirurgia bariátrica Roux-em-Y:

1) A maioria dos profissionais entrevistados não se mostrou atenta quanto à possibilidade de falha terapêutica por deficiências de absorção com esses pacientes, prescrevendo comprimidos ou cápsulas sem orientações clínicas específicas. Apesar dos profissionais mais jovens explorarem melhor outras formas farmacêuticas, estes não acompanham a evolução do paciente, enquanto os mais experientes fazem acompanhamento com o paciente.
2) Os resultados do teste de dissolução deste estudo sugerem que os fármacos de alta solubilidade não apresentam problemas de dissolução e consequentemente, na absorção, enquanto que os fármacos de baixa solubilidade estudados devem ser monitorados: Ciprofloxacina, Sulfadiazina, Atazanavir e Hidroclorotiazida, pois podem apresentar redução ou atraso na absorção e consequentemente, afetar os efeitos terapêuticos desejados.

PERSPECTIVAS FUTURAS

Pacientes bariátricos pertencem a um novo modelo populacional farmacocinético, representando novas abordagens teóricas e desafios, se utilizando de modelos computacionais fisiológicos, poucas revisões sistemáticas e estudos clínicos para demonstrar a variação do efeito farmacocinético dos medicamentos e recomendações clínicas para ingestão de formas farmacêuticas sólidas orais na tentativa de se evitar falhas terapêuticas.

Para demonstrar diferenças na biodisponibilidade oral de antibióticos, antivirais e anti-hipertensivos após cirurgia bariátrica são necessários ensaios clínicos com monitoração dos níveis plasmáticos dos fármacos.

Enquanto não há maiores evidências no manejo farmacoterapêutico e biodisponibilidade de fármacos em pacientes bariátricos, as precauções devem ser seguidas, como troca de formulação por formas líquidas ou mastigáveis, que podem ser pulverizadas ou abertas e realizar monitoramento da terapêutica, na tentativa de se contornar a possibilidade de falha terapêutica ou toxicidade, com consequências para o paciente.