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Considerations for clinical evaluation of the effects of bariatric surgery on the pharmacokinetics of orally administered drugs

Sungyeun Bae [1], **JungJin Oh** [1], **Ildae Song** [2], **Kyung-Sang Yu** [1], and **SeungHwan Lee** [1,*]

[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital, and Seoul National University College of Medicine, Seoul 03080, Korea
[2]Department of Pharmaceutical Science and Technology, Kyungsung University, Busan 48434, Korea

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***Correspondence to**
SeungHwan Lee
Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital, and Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: leejh413@snu.ac.kr

ORCID iDs
Sungyeun Bae
https://orcid.org/0000-0002-6584-9158
JungJin Oh
https://orcid.org/0000-0002-2660-4617
Ildae Song
https://orcid.org/0000-0002-3904-4735
Kyung-Sang Yu
https://orcid.org/0000-0003-0921-7225
SeungHwan Lee
https://orcid.org/0000-0002-1713-9194

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ABSTRACT

Obesity has been a growing worldwide concern, and surgical intervention including bariatric surgery is considered as one of the options for treatment. However, there still is controversy over the change in pharmacokinetics (PKs) of drugs after the surgery. To investigate the potential covariates that can influence the area under the curve (AUC) and maximum plasma concentration (C_{max}), the design of previous studies was reviewed based on pre-determined eligibility criteria. Each study calculated the ratios of the AUC and C_{max} before and after bariatric surgery. These studies investigated whether the PK parameters were affected by the time after the surgery or by the type of control group. The ratio of the AUC calculated in the early and late follow-up period was similar across Roux-en Y gastric bypass patients. No significant difference in the PK parameters was found between the pre-surgical patients and matched healthy subjects. However, certain control groups could be preferable depending on the purpose of the clinical trial. Although C_{max} was inconsistent compared to the AUC, insufficient sampling of the time points may have caused such an inconsistency. This is the first article exploring the appropriate methodology in designing clinical studies for changes in the PK characteristics of orally administered drugs in patients with bariatric surgery.

Keywords: Anastomosis, Roux-en-Y; Gastrectomy; Area Under Curve; Administration, Oral; Obesity

INTRODUCTION

Obesity has been recognized as a serious global health threat. This is a more severe problem in industrialized countries including Korea. According to the health examination provided by the Korean National Health Insurance System between 2009 and 2018, the prevalence of class I, II, and III obesity increased across all age groups and regions in both men and women [1]. Because weight reduction is known to decrease several comorbidities caused by obesity, surgical intervention like bariatric surgery is considered one of the treatment options [2,3]. Bariatric surgery, generally referring to all surgical procedures for excess weight reduction, has successfully achieved weight loss and showed improvement in hypertension,

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dyslipidemia and diabetes [4]. Consequently, European guidelines on metabolic and bariatric surgery regard patients with morbid obesity or accompanying comorbidities, such as metabolic disorders, cardio-respiratory disease, severe joint disease, and obesity-related severe psychological problems as the candidates for bariatric surgery [5]. The surgical techniques of bariatric surgery include sleeve gastrectomy (SG), biliopancreatic diversion (BPD), and Roux-en-Y gastric bypass (RYGB). Among the listed surgical techniques, SG and RYGB are the 2 most common procedures worldwide [6].

Obese patients commonly take medications due to their comorbidities. In fact, according to the 2006 National Ambulatory Care Medical Survey conducted in the United States, obese patients with BMI ≥ 30 kg/m^2 were reported to have more than 3 medications from their office-based physician visits [7]. Because bariatric surgery causes anatomical and physiological changes in the gastrointestinal (GI) tract and body composition, it may impact the pharmacokinetic (PK) profiles of concomitant drugs. The PK profiles of orally administered drugs are influenced by the processes of absorption, distribution, metabolism and excretion (ADME). Previous literature has shown that the reduced size of the stomach and bypass portions of the small intestine can affect the absorption of orally absorbed drugs [8-10]. Moreover, weight reduction after surgery can affect CYP enzyme activities and drug disposition [11]. To make matters worse, changes in the gastric emptying time and intestinal motility, increased gastric pH due to rerouting of the GI tract, reduced volumes of distribution caused by a reduced blood volume and adipose tissue and alterations in bile acid, alterations in intestinally derived hormones and the gut microbiome make it even more difficult to predict the PK characteristics of the concomitant drugs in patients after bariatric surgery. Doctors need to be cautious because alterations in the PK characteristics may increase the risk for adverse events or reduce the efficacy of the drugs.

There have been numerous clinical studies aimed at finding out how bariatric surgery affects the PK characteristics of concomitant drugs. Nonetheless, the impact of surgery on each drug seems to be different, and there has not been a definite conclusion [11]. This might be due to the variations in surgical procedures or surgeons' techniques, differences in the demographic characteristics of the enrolled patients, or the physiochemical properties of a drug. On the other hand, the PK variability could be due to an extrinsic factor: the design of the clinical trial. That is, factors such as selection of reference group, follow-up period could have contributed to inter-study variabilities. As far as we know, there have not been any articles discussing whether the design of clinical studies can influence the PK characteristics in obese patients with bariatric surgery yet. Because the appropriate methodology is crucial in achieving the goal of any clinical study, it is essential to review the clinical studies up to date and determine the factors that can interfere with the interpretation of the results. Therefore, in this paper, we explored the PK studies of orally administered drugs in obese patients with bariatric surgery. Then, we compared their results depending on the study design to discuss potential considerations for future clinical studies.

METHODS

Literature search

The literature was searched using the MEDLINE and Embase database. We searched literature from 2000 to 2021 using medical subject headings (MeSH) and text words related to bariatric surgery, PK parameters, and oral absorption (**Supplementary Data 1**). Two independent

Table 1. Eligibility criteria for screening the literature

Inclusion criteria	Exclusion criteria
Studies published after 2000 in English	Reviews, case studies, opinion pieces, editorials, conference presentation, and abstracts
Studies associated with pharmacokinetic parameters on orally administered drugs	Dietary supplements (including alcohol) and endogenous compounds
Subjects without any conditions or surgeries that can severely affect the absorption of oral drugs	Studies involving animals
Studies with the number of subjects equal to or greater than 4	Presenting neither AUC nor C_{max}

AUC, area under the curve; C_{max}, maximum plasma concentration.

researchers reviewed the searched literature whether they met the pre-determined eligibility criteria (**Table 1**). The search was confined to English language articles. Studies associated with PK parameters, especially area under the curve (AUC) and the maximum plasma concentration (C_{max}), on orally administered drugs were searched for and retrieved. Subjects with oral drug absorption problems, GI tract related cancers, or liver transplantation were all excluded from this study because it can affect intestinal motility or transporters and enzyme activities. To minimize the bias that can arise from inter-individual variabilities, only studies with the number of subjects in both the post-surgery group and the control group equal or greater than 4 were selected. Reviews, case studies, opinion pieces, editorials, conference presentations and abstracts were excluded. Studies with dietary supplements or endogenous compounds and those dealing with animals were also excluded. The eligible literature from the references of screened articles were additionally manually reviewed.

PK analysis

The main purpose of this study was to evaluate the changes in the PK parameters before and after bariatric surgery on orally absorbed drugs. Particularly, the AUC and C_{max} were compared in each study. The AUC from time 0 to last quantifiable time point (AUC_{last}) was preferred to the AUC from time 0 to infinity (AUC_{inf}) when both were presented. When the PK parameters were not shown, the AUC or C_{max} was manually estimated from the supplementary raw data. The ratio of the PK parameters was calculated as follows.

$$Ratio\ of\ PK\ Parameter\ = \frac{Mean\ PK\ Parameter\ in\ the\ Post-Surgery\ Group}{Mean\ PK\ Parameter\ in\ the\ Control\ Group}$$

There were 2 main questions to be addressed: i) Does the PK parameters change as the time since the surgery elapses, and ii) are the PK parameters influenced by the type of control group, whether the control is the pre-surgical condition of the same patients or matched healthy subjects. To answer the first question, studies with multiple follow-up periods after surgery were selected. The ratio of the PK parameters was compared between the 'early' and 'late' follow-up periods. Six months was set as the cutoff value between the early and late follow-up period because all the latter follow-up periods in the selected studies were equal to or greater than 6 months. For the second question, studies on the same drug with different control groups were compared. The control group was categorized into 'matched' if the study used healthy matching subjects and 'pre-surgery' if the study used the pre-surgery status of the patients. Furthermore, the PK parameters of the same drug with the same control group was explored to find out the reproducibility of the result.

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RESULTS

Literature search

The literature searches from MEDLINE and Embase yielded 159 articles with 28 articles published before 2000 and 71 articles considered unrelated to the topic excluded. Among the remaining 60 articles, 24 studies met the pre-defined criteria. Three additional articles were selected from the references of the screened articles. Therefore, a total of 27 studies was reviewed (**Supplementary Table 1**). Most of the studies enrolled RYGB patients and 1 study with partial gastric resection, 2 studies with BPD, and 2 studies with SG. Nine studies used healthy matching subjects as the control group. Most of them used sex and BMI as the matching variable, and 6 studies considered age as well. The number of subjects in a group ranged from 4 to 40 subjects, and only 2 studies explained the rationale for estimating the sample size. The investigated drugs were mostly medications associated with either the procedure for bariatric surgery or treatment for comorbidities of obesity.

Relationship between the PK parameters and time after surgery

To investigate the impact of the time after surgery on the changes of the PK parameters, studies with multiple follow-ups were selected. Six types of drugs from 7 studies were selected (**Table 2**) [12-18]. To minimize the possible bias by the type of bariatric surgery, only the data from the RYGB were collected. In the following studies, the changes in the PK parameters were evaluated with special considerations: i) PK parameters in Jakobsen et al. [12] were recalculated according to the method mentioned above because only the mean of the ratio of PK parameters after to before surgery was presented, and ii) the AUC_{inf} of acetaminophen was used for the analysis instead of the AUC_{last} in Chen et al. [18] because the last quantifiable time point (30 minutes) was too early considering the half-life of the administered drug (2.2 to 2.9 hours). The type of control group was 'pre-surgery' in all the selected studies.

While the AUC in the early follow-up period was similar to that in the late follow-up period, C_{max} showed a tendency to increase in the late follow-up period (**Fig. 1**, **Table 2**). Especially, the C_{max} of the immediate release (IR) form of morphine was 46% and 61% higher in the 'late' follow-up period compared to the 'early' follow-up period. Additionally, the ratio of C_{max} was more widely distributed compared to the ratio of AUC.

Table 2. Summary of the PK parameters and ratios of after to before Roux-en-Y gastric bypass surgery in each follow-up period

Author	Drug	No.	PK parameters						Ratio*			
			AUC			C_{max}			AUC		C_{max}	
			Baseline	Early	Late	Baseline	Early	Late	Early	Late	Early	Late
Jakobsen et al. [12] (2013)	Atorvastatin	12	75.0 ± 90.0	49.0 ± 24.0	36.0 ± 25.0	28.4 ± 46.2	12.8 ± 7.8	12.5 ± 14.1	0.66	0.48	0.45	0.44
Lloret-Linares et al. [13] (2014)	Morphine IR	24–30	41.8 ± 13.0	48.2 ± 14.8	55.1 ± 28.1	16.9 ± 7.6	21.5 ± 10.0	34.6 ± 19.0	1.15	1.32	1.27	2.05
Chan et al. [14] (2015)	Digoxin	9	13.00 ± 2.50	14.60 ± 3.80	14.30 ± 2.90	3.08 ± 1.38	3.05 ± 0.85	3.41 ± 1.13	1.12	1.10	0.99	1.11
	Midazolam		20.80 ± 10.70	20.30 ± 10.80	18.30 ± 7.90	9.67 ± 6.72	16.09 ± 6.65	16.56 ± 7.55	0.98	0.88	1.66	1.71
Goday Arno et al. [15] (2017)	Acetaminophen	14	11.20 ± 4.51	15.80 ± 5.23	16.40 ± 3.32	5.21 ± 2.45	6.78 ± 2.64	8.13 ± 2.97	1.41	1.46	1.30	1.56
Lloret-Linares et al. [16] (2017)†	Morphine IR	16–25	154	189	200	49	71	104	1.23	1.30	1.45	2.12
Ginstman et al. [17] (2019)	Desogestrel	9–10	6.097 ± 1.490	6.119 ± 1.560	6.096 ± 1.410	0.590 ± 0.236	0.633 ± 0.113	0.817 ± 0.163	1.00	1.00	1.07	1.38
Chen et al. [18] (2020)†	Acetaminophen	10	53.0 ± 15.2	82.4 ± 24.9	81.3 ± 28.0	18.5 ± 7.2	36.5 ± 6.9	36.6 ± 11.9	1.55	1.53	1.97	1.98

Values are given as the mean ± standard deviation. Baseline indicates the pre-surgery status.
PK, pharmacokinetic; AUC, area under the curve; C_{max}, maximum plasma concentration; IR, immediate release.
*Ratio of PK parameters after to before surgery; †AUC from time 0 to infinity was presented.

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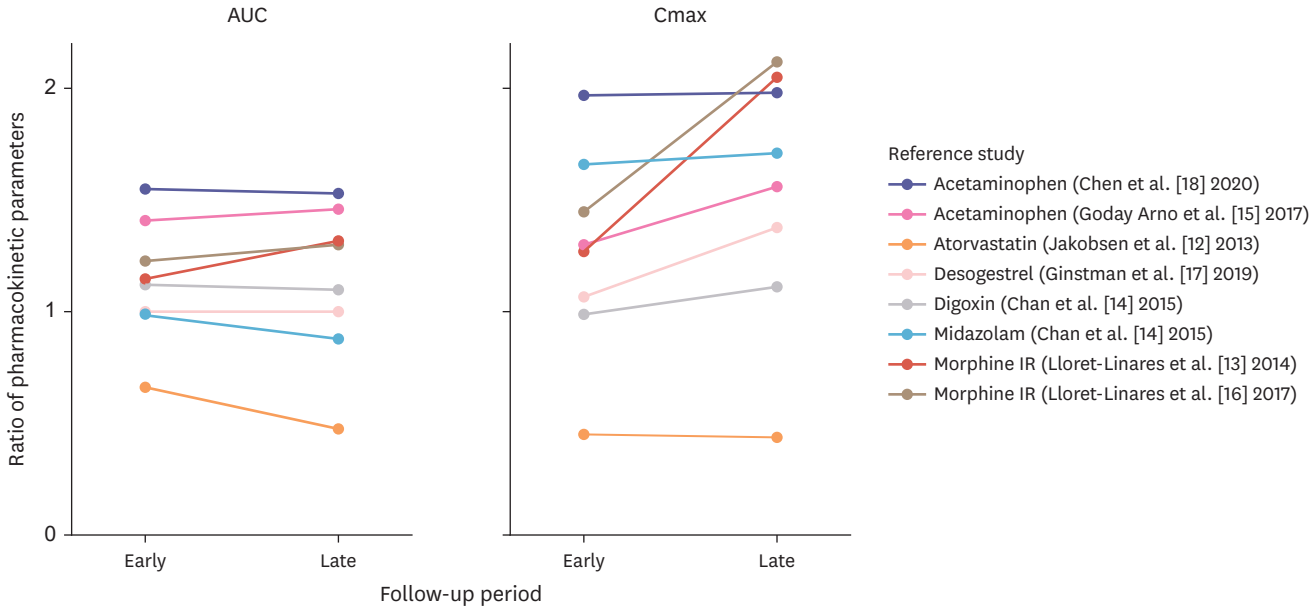

Figure 1. Comparison of the ratio of pharmacokinetic parameters of after to before Roux-en-Y gastric bypass surgery according to follow-up period. Follow-up period was categorized into 'early' (< 6 months) and 'late' phases (≥ 6 months) defined by the time after the surgery.
IR, immediate release.

Table 3. Summary of the PK parameters and ratios of after to before Roux-en-Y gastric bypass surgery according to the control group

Author	Control group	Drug	PK parameters				Ratio*	
			AUC		C_{max}		AUC	C_{max}
			Control	Post-surgery	Control	Post-surgery		
Tandra et al. [19] (2013)		Omeprazole	0.8 ± 4.5	0.8 ± 0.7	230.0 ± 871.0	441.0 ± 247.0	1.00	1.92
		Midazolam	6.0 ± 23.0	3.4 ± 2.5	2.7 ± 11.0	1.9 ± 1.6	0.57	0.70
Hachon et al. [21] (2017)	Matched	Morphine SR	80	66	16	11	0.83	0.69
Ginstman et al. [23] (2020)		Levonorgestrel	17.00 ± 8.10	19.90 ± 7.10	2.96 ± 1.17	3.34 ± 1.16	1.17	1.13
Moreira de Brito et al. [25] (2021)		Levonorgestrel	6,345.6 ± 2,012.8	7,711.8 ± 2,831.2	1,855.3 ± 616.2	1,909.5 ± 741.9	1.22	1.03
Lloret-Linares et al. [13] (2014)		Morphine IR	41.8 ± 13.0	55.1 ± 28.1	16.9 ± 7.6	34.6 ± 19.0	1.32	2.05
Chan et al. [14] (2015)		Midazolam	20.80 ± 10.70	18.30 ± 7.90	9.67 ± 6.72	16.56 ± 7.55	0.88	1.71
Gesquiere et al. [20] (2015)		Metoprolol IR	2,373	3,206	404	532	1.35	1.32
		Metoprolol CR	1,917	2,333	-	-	1.22	-
Goday Arno et al. [15] (2017)		Acetaminophen	11.20 ± 4.51	16.40 ± 3.32	5.21 ± 2.45	8.13 ± 2.97	1.46	1.56
Lloret-Linares et al. [16] (2017)†	Pre-surgery	Morphine IR	154	200	49	104	1.30	2.12
Puris et al. [22] (2019)		Omeprazole	228.0	270.0	82.9	139.0	1.18	1.68
		Midazolam	20.30	15.10	6.76	5.42	0.74	0.80
Chen et al. [18] (2020)		Acetaminophen	53.0 ± 15.2	81.3 ± 28.0	18.5 ± 7.2	36.6 ± 11.9	1.53	1.98
Yska et al. [24] (2020)		Metoprolol IR	391 ± 144	446 ± 168	96 ± 33	119 ± 53	1.14	1.24
		Metoprolol CR	361 ± 159	225 ± 137	-	-	0.62	-

Values are given as the mean ± standard deviation.
PK, pharmacokinetic; CR, controlled release; IR, immediate release; SR, sustained release.
*Ratio of PK parameters in post-surgery to control; †AUC from time 0 to infinity was presented.

Relationship between the PK parameters and the type of control group

To investigate the impact of the type of control group on the changes of the PK parameters, drugs studied in multiple articles were selected. To minimize the bias from the follow-up period and type of surgery, only data with a follow-up period equal to or greater than 6 months after RYGB were included. Six types of drugs from 12 studies were selected (**Table 3**) [13-16,18-25]. As mentioned above, the AUC of acetaminophen in Chen et al. was analyzed in the AUC_{inf} instead of the AUC_{last}.

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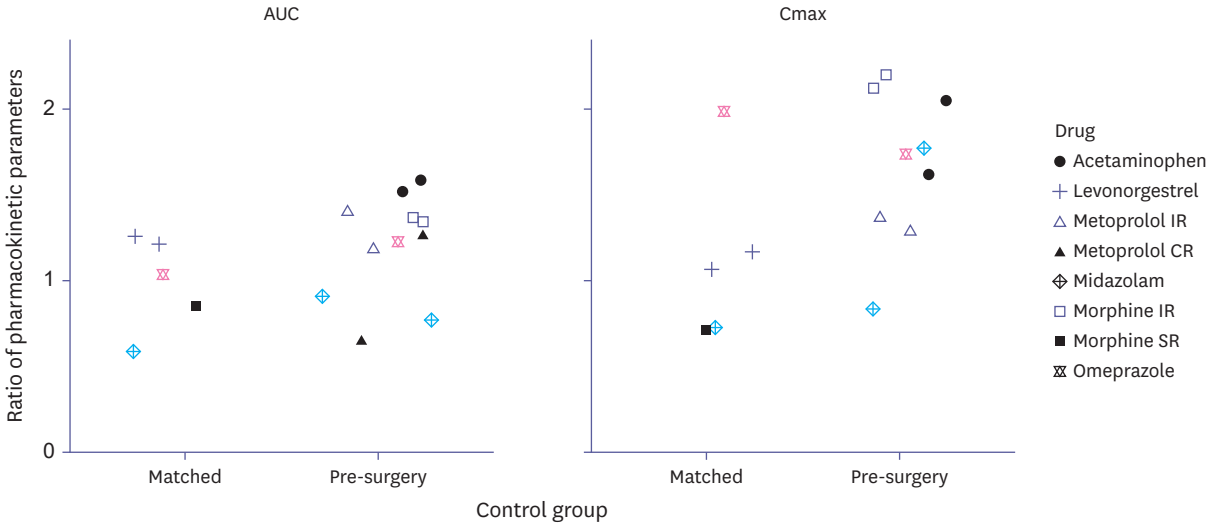

Figure 2. Comparison of the ratio of pharmacokinetic parameters of after to before Roux-en-Y gastric bypass surgery according to the type of control group. The colored figures represent the drugs studied in both the studies with the pre-surgical condition of the same patients and the matched healthy subjects as the control group.
IR, immediate release; CR, controlled release; SR, sustained release.

The ratio of PK parameters of the same drug was similar within the same type of control group except for the C_{max} of midazolam in the 'pre-surgery' group (**Fig. 2**, **Table 3**). Meanwhile, the changes of the PK parameters were influenced by the type of release form. For example, the ratio of the PK parameters in sustained release form of morphine decreased after surgery while the opposite result was observed in the IR form. The PK parameters of the IR form of metoprolol increased after surgery in 2 studies while the ratio of the AUC in the controlled release (CR) form of metoprolol increased in one study and decreased in another. The ratio of the PK parameters in omeprazole were similar between studies with a 'matched' and 'pre-surgery' control group. The ratio of the AUC in midazolam was also similar between studies with a 'matched' and 'pre-surgery' control group.

DISCUSSION

Generally, AUC and C_{max} are associated with the efficacy and toxicity of a particular drug. Therefore, the changes in the AUC and C_{max} after surgery were explored in this study. For orally absorbed drugs, both the AUC and C_{max} can be influenced by the anatomical and physiological changes by the bariatric surgery. In order to investigate the impact of bariatric surgery on the PK parameters, many trials, especially with the drugs frequently used in patients with obesity or during the bariatric surgery, were implemented. Obviously, weight loss is observed after bariatric surgery. However, there are other factors affecting the ADME of a particular drug and thus, a drug-by-drug risk assessment was recommended in a recent article [26]. Reviewing previous literature, we determined that the design of the clinical studies was heterogeneous and wondered if the clinical design could have affected the evaluation of the changes for the PK characteristics.

In our study, we found out that C_{max} is more variable and more affected by time after surgery or by the type of control group compared to the AUC. This might be explained by the anatomical and physiological changes after bariatric surgery. Notably, the relationship

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between the time to reach peak concentration (T_{max}) and C_{max} are well described in previous literature. McLachlan et al. [9] discussed that the change in transit time through the stomach and weight loss with consequent changes in body composition can contribute to the decrease in T_{max} accompanied by an increase in the C_{max} after bariatric surgery, and similar comments were also found in another review article [26]. Meanwhile, C_{max} is an observed value and is largely dependent on the sampling time. That is, C_{max} cannot be properly measured if sampling is not done with the appropriate timing. For instance, in the case of midazolam, the T_{max} was estimated to be around 0.26 hours 12 months after RYGB in Chan et al. [14], but only one sampling point was arranged in Tandra et al. [19] before 0.26 hours. Even worse, the first sampling point was set 1 hour after administering midazolam in Puris et al. [22]. Even though the C_{max} was shown to decrease after RYGB in Tandra et al. [19] and Puris et al. [22], the result might have been different if more sampling points were arranged before the expected T_{max}. This is more convincing in that the C_{max} of morphine after intravenous infusion increased after RYGB in Tandra et al. [19] from 6.5 to 10 ng/mL, and the ratio is similar to the ratio shown in Chan et al. [14]. This might explain why the C_{max} in the CR form of metoprolol showed varying results: plasma samples around the expected T_{max} were more collected in Gesquiere et al. [20] compared to Yska et al. [24]. Therefore, aggressive sampling is recommended around the expected T_{max}, especially before the expected T_{max} because the T_{max} is likely to be shortened after bariatric surgery, to evaluate T_{max} more precisely.

On the other hand, the AUC showed more consistent and stable results according to the time after surgery. This might be due to the fact that the AUC is calculated through concentrations in multiple time series and is less likely to be affected by the sampling points compared to C_{max}. From a different point of view, the AUC is influenced by multiple factors [9] and might be resistant to dramatic changes. Additionally, the bioavailability and clearance of midazolam in patients 1 year after RYGB were not significantly different between the matched control in Tandra et al. [19]. Indeed, the lean body mass and basal metabolic rate was reported to be consistent from 6 to 12 months after bariatric surgery and the intestinal adaptation affecting the AUC might be completed within 6 months after RYGB [27]. If the pharmacologic action of a particular drug is AUC-dependent, a follow-up of therapeutic drug monitoring until 6 months after RYGB might be sufficient.

In studies that used healthy subjects as the control group, sex, BMI and age were considered as the possible covariates in most cases, and race was additionally considered in one of the studies. Generally, the PK parameters were not affected whether the control group was 'matched' or 'pre-surgery'. However, there are some points to be considered depending on the study objective. In Tandra et al. [19], large inter-individual variability in the AUC and C_{max} was observed in the 'matched' control group. This might be due to the different distribution in CYP enzyme phenotypes between the healthy controls and the patients after bariatric surgery. In this case, using a 'pre-surgery' control might be more appropriate. Obviously, when multiple follow-ups after surgery are needed, using a 'pre-surgery' control seems more appropriate as seen in all the studies with multiple follow-ups among the reviewed literature because it can guarantee more power with the same number of subjects statistically. Furthermore, when designing a clinical study with a modified release form of a particular drug, the impact by anatomical and physiologic changes after bariatric surgery must be considered. The PK result can vary depending on the type of control as observed in the different release forms of metoprolol and morphine.

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Aforementioned in the previous articles, the altered PK characteristics do not necessarily correlate with a change in therapeutic effects or dose adjustment [10]. Even though they evaluated the pharmacodynamics (PD) in 2 studies [19,28], it might be practically difficult to check the PD markers in patients with bariatric surgery. Therefore, it is important to carefully merge the known PK-PD relationship of a particular drug with the PK data from clinical studies to determine whether a dose adjustment would be necessary.

There are some limitations in this study. The mean PK parameters were presented as the geometric mean in some studies and the arithmetic mean in the others so the interpretation could be mixed up. The technological improvement in bariatric surgery over 20 years could have influenced the PK profiles. Additionally, most of the trials were limited to RYGB patients. The PK characteristics of acetaminophen after SG were similar to those of RYGB in Goday Arno et al. [15], but the ratio of the PK parameters was higher in Porat et al. [29]. Because there is a growing popularity for SG due to its less overall chronic malabsorption effects [8, 30], more studies on SG would be crucial for post-surgical pharmacotherapy considerations.

In summary, the AUC showed consistent results and was not influenced by the time after surgery. The type of control did not affect the PK parameters, but a certain type of control can be preferable in special occasions. The changes in the PK parameters do not necessarily require a dose modification, but the drug dose should be decided based on the PK-PD relationship of the drug of interest.

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Search strategy

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Supplementary Table 1
Overall characteristics of the reviewed articles

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Supplementary References

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