Clinical guidance for dosing and monitoring oral antihormonal drugs in patients with breast cancer after Roux-en-Y gastric bypass

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Clinical Guidance for Dosing and Monitoring Oral Antihormonal Drugs in Patients with Breast Cancer After Roux-en-Y Gastric Bypass

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Abstract: Obesity is associated with an increased risk of cancers, such as breast cancer. Roux-en-Y gastric bypass (RYGB) is a common surgical intervention used to induce weight loss, reduce comorbidities, and improve overall survival. Due to alterations in the gastrointestinal tract, RYGB is associated with changes in oral drug disposition, which can affect treatment outcomes. Oral antihormonal agents were monitored in 9 patients who previously underwent RYGB. The results of therapeutic drug monitoring and estradiol concentrations were analyzed, and a review of the relevant literature was performed. As only 1 of the 6 patients prescribed tamoxifen achieved a therapeutic endoxifen concentration with the standard dose of 20 mg/d, a higher starting dose of 40 mg/d was recommended to increase the probability of attaining a therapeutic plasma concentration. All patients with decreased CYP2D6 metabolic activity could not achieve therapeutic plasma concentrations; therefore, CYP2D6 genotyping was recommended before the initiation of tamoxifen therapy to identify patients who should be switched to aromatase inhibitors. Anastrozole and letrozole exposure in patients who underwent RYGB patients appeared sufficient, with no dose adjustment required. However, until more data become available, monitoring aromatase inhibitor efficacy is recommended. Monitoring the drug concentrations is a viable option; however, only indicative data on therapeutic drug monitoring are available. Therefore, estradiol concentrations should be measured.

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INTRODUCTION

Obesity is associated with an increased risk of cancers, such as breast cancer, which is the most prevalent type.[1,2] This increased risk may be due to several (patho)physiological changes, such as increased hypoxia and inflammation in obese adipose tissue and the catalysis of estrogen synthesis owing to increased aromatase expression and activity, especially in postmenopausal women. Weight loss is proven to reduce the risk and mortality rates of postmenopausal patients with breast cancer.[3] Bariatric surgery also reduces the risk of breast cancer compared with nonsurgical obesity controls (0.54% versus 0.84%, respectively).[4]

Currently, bariatric surgery is the most effective long-term weight loss treatment for morbidly obese people [those with a body mass index (BMI) of at least 40 kg/m^2] and obese people (with a BMI between 35 and 40 kg/m^2) who have 1 or more comorbidities.[5] One of the most common bariatric surgery techniques is the "Roux-en-Y" gastric bypass (RYGB). For RYGB, a small gastric pouch is introduced and is connected to the lower part of the intestine, bypassing the small intestine and biliary limb. This technique is associated with many physiological changes, such as alterations in gastric pH, changes in transit time, delayed exposure to bile salts, smaller intestinal absorption area, and several nutritional deficiencies.[6,7]

These bypass-related changes may in turn lead to changes in oral drug disposition, which can be hard to predict based on drug properties alone.[7,8] For example, the biopharmaceutics classification system, which divides drugs into 4 classes according to their physicochemical solubility and permeability characteristics, has proven to be inappropriate for consistent prediction of oral absorption for all classes after bariatric surgery.[6] For some drugs that are metabolized by specific pathways, relevant information is available on the reversibility of obesity-related changes after bariatric surgery. For example, the activity of CYP3A4, a hepatic enzyme system responsible for the metabolism of many drugs, is known to be lower in patients with obesity due to chronic inflammation and/or steatosis.[9] After bariatric surgery or extensive weight loss, both inflammation and steatosis can be reversed, possibly leading to recovery in CYP3A4 activity and other

liver-related processes, such as hepatic flow.[10] For midazolam, a well-known probe drug for CYP3A4 activity, clearance is reported to increase after bariatric surgery,[11] despite no relevant changes in oral bioavailability.[11]

The administration of oral antihormonal drugs to patients with hormone receptor–positive breast cancer is crucial to minimizing breast cancer recurrence. However, adequate exposure must be achieved. Due to potentially relevant variations in pharmacokinetics after bariatric surgery and their potential variations over time,[12,13] a study on the pharmacokinetics of oral drugs and monitoring of the efficacy of these drugs, or application of therapeutic drug monitoring (TDM), is generally recommended to ensure safe and effective treatment.

An exposure-efficacy analysis of tamoxifen revealed that an endoxifen (the main metabolite of tamoxifen) steady-state trough concentration of at least 5.97 ng/mL is associated with a 26% reduced chance of recurrence.[14] Because CYP2D6 is involved in the metabolism of tamoxifen, CYP2D6 intermediate (IM) or poor metabolizers (PM) or users of moderate and strong CYP2D6 inhibitors (eg, fluoxetine) exhibit lower endoxifen plasma concentrations.[15] A definitive exposure-efficacy target has not been established for the aromatase inhibitors. However, for each of these individual agents, indicative data are available from TDM. According to a prospective study, the anastrozole trough level (<34.2 ng/mL) in patients with stable or increased estradiol concentrations is significantly lower than that in those with decreased estradiol concentrations.[16,17] This concentration is close to the population median of 33.2 ng/mL, which suggests that even a large portion of the population, without bariatric surgery, has subtherapeutic concentrations.[17] For letrozole, an exposure-efficacy analysis revealed a trend of increased time to progression in patients with letrozole-trough concentrations above 85.6 ng/L.[17] This level is also close to the population median of 89.7 pg/mL.[18] For oral antihormonal drugs administered for breast cancer, TDM is not widely implemented in daily clinical practice due to ambiguous data on relations between exposure and efficacy. However, until larger studies are available regarding the efficacy and safety of oral drugs in the bariatric surgery population, TDM in individual patients is indicated to monitor this special population and ensure efficacy.

In this study, we sought to describe 9 patients treated with oral antihormonal agents for breast cancer after RYGB at our clinical practice. According to the standard clinical practice at our hospital, these patients were subjected to thorough monitoring because limited evidence is available on the absorption of these orally administered drugs after bariatric surgery. The data were collected retrospectively. We also performed a review of the literature on oral antihormonal agents for breast cancer among bariatric patients. Finally, we presented some guidance on the dosing and monitoring of antihormonal breast cancer agents in this patient population.

CASE SERIES

Case 1

A 53-year-old postmenopausal woman with a BMI of 25.2 kg/m^2 was diagnosed with stage IA ER/PR + HER2− breast cancer. After breast conserving surgery, she was prescribed 20 mg/d of tamoxifen. The patient underwent RYGB 1 year earlier. To ensure adequate exposure, the endoxifen plasma concentration was monitored. A 20 mg/d dose of tamoxifen resulted in a steady-state endoxifen plasma concentration of 5.0 ng/mL (target >5.96 ng/mL).[14] The patient did not use CYP2D6-inhibiting drugs, and CYP2D6 genotyping was not performed. Thus, the dose was increased to 40 mg/d, resulting in a steady-state endoxifen plasma concentration of 8.44 ng/mL.

Case 2

A 50-year-old postmenopausal woman with a BMI of 33.5 kg/m^2 was diagnosed with stage IIIA ER/PR + HER2−breast cancer. She received neoadjuvant chemotherapy followed by a modified radical mastectomy and radiotherapy. Subsequently, adjuvant chemotherapy with 20 mg/d of tamoxifen was initiated. The patient had undergone RYGB 7 years before therapy initiation. To ensure adequate exposure to tamoxifen, the endoxifen plasma concentration was monitored. Endoxifen monitoring revealed a steady-state plasma concentration of 3.8 ng/mL (target >5.96 ng/mL).[14] The tamoxifen dose was increased to 30 mg/d and the endoxifen concentration increased to 5.0 ng/mL. A subsequent increase to 40 mg/d resulted in a steady-state concentration of 8.3 ng/mL. The patient did not use CYP2D6-inhibiting drugs and CYP2D6 genotyping was not performed.

Case 3

A 51-year-old postmenopausal woman with a BMI of 25.5 kg/m^2 was diagnosed with breast cancer, and administered neoadjuvant chemotherapy. She underwent ablation and received radiotherapy and antihormonal therapy with 20 mg/d of tamoxifen. Four years later, she underwent RYGB to induce weight loss. To monitor tamoxifen efficacy, endoxifen blood concentrations were monitored. A 20 mg/d dose of tamoxifen resulted in a steady-state endoxifen plasma concentration of 5.26 ng/mL (target >5.96 ng/mL).[14] As a result, the tamoxifen dose was increased to 40 mg/d. Follow-up monitoring of endoxifen concentration was not deemed necessary. The patient did not use CYP2D6-inhibiting drugs, and CYP2D6 genotyping was not performed.

Case 4

A 52-year-old premenopausal woman with a BMI of 30.8 kg/m^2 was diagnosed with stage IA ER/PR + HER2− breast cancer. She underwent breast-conserving surgery followed by radiotherapy and was prescribed 20 mg/d of tamoxifen. She had undergone RYGB 5 years earlier. To ensure adequate exposure to tamoxifen, the endoxifen plasma concentration was monitored. A tamoxifen dose of 20 mg/d resulted in a steady-state endoxifen plasma concentration of 13.3 ng/mL (target >5.96 ng/mL).[14] The patient did not use CYP2D6-inhibiting drugs, and CYP2D6 genotyping was not performed.

Case 5

A 62-year-old postmenopausal woman with a BMI of 29.6 kg/m^2 was diagnosed with stage IA ER/PR + HER2-breast cancer with high clinical risk. She underwent breast-conserving surgery and adjuvant chemotherapy. She was prescribed 20 mg/d of tamoxifen. The patient had undergone RYGB 3 years earlier. Three months after the initiation of tamoxifen therapy, the steady-state plasma concentration of endoxifen was 1.5 ng/mL (target: >5.96 ng/mL).[14] As a result, the tamoxifen dose was increased to 40 mg/d. After the increase, an endoxifen steady-state plasma concentration of 3.9 ng/mL was observed. The patient did not use CYP2D6-inhibiting drugs. To rule out the possibility that this low concentration was due to

surgery or whether an altered CYP2D6 genotype had contributed, a CYP2D6 genotyping was performed. This analysis revealed a PM phenotype (*CYP2D6 *4/*10*). Therefore, the patient was switched to 2.5 mg/d of letrozole, and the letrozole steady-state trough concentration was measured. The letrozole trough concentration was 93.7 μg/L (target >85.6 μg/L).[17,19] To confirm adequate estradiol suppression, the estradiol concentration was monitored using a sensitive 2-dimensional liquid chromatography tandem mass spectrometry (2D-LC-MS/MS) assay [lower limit of quantification (LLOQ) of 6 pmol/L]. The estradiol concentration was below the LLOQ of the assay.

Case 6

A 49-year-old premenopausal woman with a BMI of 43.1 kg/m^2 was diagnosed with stage 2 ER/PR+ and HER2− breast cancer. She was prescribed 40 mg/d of tamoxifen (ie, double the standard dose) combined with intravenous chemotherapy. She had undergone RYGB 12 years earlier. To ensure adequate exposure of tamoxifen, the endoxifen plasma concentration was monitored, which revealed a steady-state endoxifen plasma of 4.0 ng/mL (target >5.96 ng/mL).[14] The patient did not use CYP2D6-inhibiting drugs. To assess whether this low concentration was due to surgery or an altered CYP2D6 genotype, a CYP2D6 genotyping was performed. CYP2D6 genotyping revealed that the patient was an IM (*CYP2D6 *5/*41*). As a further dose increase was not expected to result in a therapeutic plasma concentration, the patient was switched to an aromatase inhibitor.

Case 7

A 49-year-old postmenopausal woman was diagnosed with stage 2 breast cancer was administered neoadjuvant chemotherapy. Subsequently, she underwent ablation and received radiotherapy and antihormonal therapy with anastrozole. Six years after the primary diagnosis of breast cancer, she underwent RYGB to induce weight loss. At the time of surgery, she was using 1 mg/d of anastrozole. To monitor anastrozole efficacy, both anastrozole and estradiol blood concentrations were monitored before and 1 month after bariatric surgery. The anastrozole steady-state trough concentration changed from 31 pg/mL presurgery to 53 pg/mL postsurgery (for comparison, the mean trough concentration in the reference population is 33.2 pg/mL),[17,19] suggesting adequate absorption. To confirm adequate estradiol suppression, estradiol concentrations were analyzed using 2D-LC-MS/MS. Both presurgery and postsurgery estradiol concentrations were below the LLOQ of 6.0 pmol/L. The corresponding presurgery and postsurgery BMIs at the time of the TDM were 43.9 and 40.6 kg/m^2, respectively.

Case 8

A 51-year-old postmenopausal woman with stage 1A ER/PR+ and HER2+ lobular breast cancer received antihormonal therapy with a daily dose of 1 mg of anastrozole. She had undergone RYGB 7 years earlier to induce weight loss. Her BMI at the start of anastrozole treatment was 44.4 kg/m^2. To monitor anastrozole efficacy, its concentration in the blood was monitored. The steady-state anastrozole trough concentration was 19.5 pg/mL (mean trough concentration in the reference population is 33.2 pg/mL),[17,19] which may be due to reduced absorption, although wide interpatient variability is known.[20] To ensure adequate efficacy, estradiol plasma concentrations were monitored, which were below the LLOQ of 6.0 pmol/L.

Case 9

A 61-year-old postmenopausal woman with stage 1A ER/PR+ and HER2− breast cancer received antihormonal therapy with 1 mg/d of anastrozole. She had undergone RYGB 4 years earlier to induce weight loss. Her BMI at the start of anastrozole treatment was 24.5 kg/m^2. To monitor anastrozole efficacy, anastrozole blood concentrations were monitored. The steady-state anastrozole trough concentration was 14.8 pg/mL (for comparison, the mean trough concentration in the reference population is 33.2 pg/mL),[17,19] which may be due to reduced absorption, although wide interpatient variability is known.[20] Subsequently, to ensure adequate efficacy, estradiol concentrations were monitored and found to be below the LLOQ of 6.0 pmol/L.

The patient observations are summarized in Table 1.

DISCUSSION AND REVIEW OF THE LITERATURE

Nine patients with breast cancer who underwent RYGB were treated with oral antihormonal agents. Due to physiological changes after RYGB, absorption of the orally administered drugs may be affected. Therefore, according to routine clinical practice in our clinic, we measured drug concentrations (TDM), and a pharmacodynamic parameter (estradiol) when applicable, to monitor possible impaired absorption. Here, we aimed to discuss these cases by evaluating the antihormonal agents separately. In addition, we performed a review of the literature on the subject.

In our case series, only 1 of the 6 patients (17%) treated with tamoxifen achieved an adequate endoxifen plasma concentration with the standard tamoxifen dose of 20 mg/d. Compared with a non-RYGB population, this result is highly aberrant. For example, in the TOTAM study, 80% of patients achieved a therapeutic endoxifen plasma concentration with a tamoxifen dose of 20 mg/d, defined as a concentration above the threshold of 16 nM (ie, 5.97 ng/mL). After TDM-guided dose escalation (to 30 or 40 mg, depending on the endoxifen level), 89% of all patients in the TOTAM study attained a therapeutic endoxifen level.[21] In our case series, only 66% of patients attained a therapeutic concentration with a tamoxifen dose of 40 mg/d, which is lower than the 89% shown in the TOTAM study.[21] This result suggests that tamoxifen absorption might be hampered after bariatric surgery, leading to lower endoxifen concentrations than that in the non-RYGB population. These findings also align with those of Wills et al, who found subtherapeutic endoxifen concentrations with a tamoxifen dose of 20 mg/d after RYGB. For 1 of their patients, the dose was increased to 40 mg/d, resulting in a therapeutic endoxifen concentration.[22] No other literature is available on the use of tamoxifen after bariatric surgery.

In our case series, both patients with subtherapeutic endoxifen concentrations who received a tamoxifen dose of 40 mg/d after TDM-guided dosing had an affected CYP2D6 allele. One patient had a PM phenotype, whereas the other had an IM phenotype. Overall, 33% of patients had an affected CYP2D6 allele, which aligns with the results of the TOTAM study, in which 36% of patients had an affected CYP2D6 allele. Of note, we found 1 PM CYP2D6 phenotype (17%), indicating a higher occurrence of the PM phenotype than that reported in the TOTAM study (7.6%) and a higher percentage than that reported for the normal population. In a healthy volunteer population from the Netherlands, the prevalence of CYP2D6 IM was 30.5% and the incidence of

TABLE 1. Summary of Patient Observations After Roux-en-Y Gastric Bypass Surgery

Case ID	Drug	TDM	Other Laboratory Findings	BMI (kg/m^2)
1	Tamoxifen	Therapeutic concentration with a dose of 40 mg per day	—	25.2
2	Tamoxifen	Therapeutic concentration with a dose of 40 mg per day	—	33.5
3	Tamoxifen	Therapeutic concentration with a dose of 40 mg per day	—	25.5
4	Tamoxifen	Therapeutic concentration with a dose of 20 mg per day	—	30.8
5	Tamoxifen	Subtherapeutic concentration with a dose of 40 mg per day	CYP2D6 PM	29.6
	Letrozole	Concentration above the median of the population with a dose of 2.5 mg per day	Adequate estradiol suppression	
6	Tamoxifen	Subtherapeutic concentration with a dose of 40 mg per day	CYP2D6 IM	43.1
7	Anastrozole	Concentration above the median of the population with a dose of 1 mg per day	Adequate estradiol suppression	40.6
8	Anastrozole	Concentration below the median of the population with a dose of 1 mg per day	Adequate estradiol suppression	33.2
9	Anastrozole	Concentration below the median of the population with a dose of 1 mg per day	Adequate estradiol suppression	24.5

CYP2D6 PM was 5.5%.[23] This result could be due to the small size of our study or could indicate that the CYP2D6 PM genotype is more prevalent in a morbidly obese population. As the other patients achieved therapeutic concentrations with a dose of 40-mg tamoxifen per day, these patients are not expected to have a CYP2D6 PM genotype. Therefore, no genotyping was performed in these patients.

Four patients were treated with aromatase inhibitors: 3 with anastrozole and 1 with letrozole. In all patients, the plasma concentration of the drugs was measured, including the estradiol concentration, which served as a pharmacodynamic parameter. Drug exposure was considered adequate if the drug concentration was above the median concentration in the population (ie, the threshold). Two patients, both on anastrozole, had inadequate exposures, whereas the other 2 patients had adequate exposures. However, estradiol suppression was adequate in all 4 patients because the estradiol concentrations were below the LLOQ of the assay (6 pmol/L).

Literature on anastrozole and letrozole efficacy in patients after bariatric surgery is scarce. One case report described a 33-year-old man with secondary azoospermia and primary testicular failure with testosterone deficiency, 8 months after sleeve gastrectomy.[24] He was treated with 1 mg/d of anastrozole for 10 months and achieved adequate androgenization based on the total testosterone concentration (248–441 pg/mL). The estradiol concentrations decreased from 94.7 to <18 pmol/L within 3 months of starting anastrozole. In another case, a 53-year-old woman with a history of RYGB and use of anastrozole had joint and muscle pain, which are common adverse reactions to anastrozole, suggesting adequate exposure.[22] Both reports suggest adequate absorption and possible efficacy in the sleeve gastrectomy case. For letrozole, no published reports were found.

Based on our observations, we opted to provide several recommendations for dosing and monitoring oral antihormonal drugs in patients with breast cancer after RYGB (Table 2). As only 1 of the 6 patients administered with tamoxifen achieved a therapeutic endoxifen concentration with the standard dose of 20 mg per day, we recommend a higher starting dose to increase the probability of attaining a therapeutic plasma concentration. With a dose of 40 mg per day, 66% of our patients had a therapeutic plasma concentration. An important argument for using an increased initial dose instead of slowly titrating doses using TDM is the time taken by endoxifen to reach steady-state conditions (ie, approximately 3 months). Therefore, suboptimal initial dosing would unnecessarily lead to subtherapeutic exposure during the first 3 months. Therefore, we recommend an initial dose of 40 mg per day, followed by TDM after 3 months. Higher doses of tamoxifen are not associated with an increased frequency of

TABLE 2. Summary of Recommendations

Drug	Clinical Guidance on Dosing and monitoring
Tamoxifen	(1) Perform CYP2D6 genotyping to identify PM and IM patients who need to be switched to aromatase inhibitors
	(2) In EM patients: Start with a daily dose of 40 mg and uptitrate/downtitrate the dose using steady-state endoxifen concentrations
	(3) Repeat at 6 and 12 months after surgery
Anastrozole	(1) Start with a daily dose of 1-mg anastrozole
	(2) Confirm adequate estradiol suppression* in obese patients
	(3) In nonobese RYGB patients, another approach could be considered: monitoring the anastrozole steady-state trough concentration. Confirm adequate estradiol suppression* in cases where the anastrozole concentration is below 34.2 pg/mL
	(4) Repeat at 6 and 12 months after surgery
Letrozole	(1) Start with a daily dose of 2.5-mg letrozole
	(2) Confirm adequate estradiol suppression* in obese patients
	(3) In nonobese patients, another approach could be considered: monitoring the letrozole steady-state trough concentration. Confirm adequate estradiol suppression* in cases where the letrozole concentration is below 85.6 pg/mL
	(4) Repeat at 6 and 12 months after surgery

*Using an analytical method, eg, LC-MS/MS with a low LLOQ (preferably 5 pmol/L or lower).

adverse events.[25,26] Research is available on increasing tamoxifen doses up to even 120 mg per day.[17] However, a dose increase beyond 40 mg per day was not performed for our patients.

Extra caution is required when prescribing tamoxifen to patients who have a CYP2D6 IM or PM phenotype and/or are using strong CYP2D6 inhibitors (eg, fluoxetine). Two of the 6 patients (33%) had a CYP2D6 genotype corresponding to decreased metabolic activity. In these patients, even with a 40-mg dose, a therapeutic plasma concentration could not be reached. Current oncology guidelines, such as the National Comprehensive Cancer Network and American Society of Clinical Oncology, do not recommend CYP2D6 genotyping before tamoxifen use. According to the FDA label, the impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established, and PMs have lower endoxifen concentrations. The Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2D6 and tamoxifen therapy provides alternatives for tamoxifen use when the genotype is known before the start of tamoxifen therapy.[15] After bariatric surgery, malabsorption was found to occur, and patients with aberrant CYP2D6 genotypes could not reach therapeutic plasma concentrations. Therefore, we recommend CYP2D6 genotyping before the initiation of tamoxifen therapy. If a CYP2D6 IM or PM genotype is revealed, we recommend an alternative treatment. The recommendations for dosing and monitoring tamoxifen are summarized in Table 2.

All patients administered the standard recommended dosage of aromatase inhibitor therapy had adequate estradiol suppression, defined as an estradiol concentration below the LLOQ of 6 pmol/L. Although our evidence is limited by the small sample size, we showed that anastrozole and letrozole exposure in patients who underwent RYGB may be sufficient, with no dose adjustments required. Until more data become available, we recommend monitoring the efficacy of aromatase inhibitors.

Monitoring drug concentrations is a viable option. However, obese patients are known to have higher levels of aromatase enzyme activity.[27–29] This increased level may be associated with aromatase inhibitors failing to achieve sufficient estradiol depletion, possibly leading to an increased risk of breast cancer recurrence.[30,31] Therefore, we recommend measuring estradiol concentrations in post-RYGB patients who are (still) obese. These levels should be monitored using an assay that is sensitive enough to detect the very low concentrations of estradiol present during aromatase inhibitor therapy.[16,32,33] In the ALIQUOT study, the mean estradiol concentrations in patients without morbid obesity postanastrozole and postletrozole were 2.5–3.2 pmol/L and 1.4–2.0 pmol/L, respectively.[33] However, because the LLOQ of the assay was only 3 pmol/L, the reported concentrations were extrapolated below the LLOQ.[33] The 2D-LC-MS/MS assay used for estradiol has an LLOQ of 6 pmol/L. This value is lower than that of the conventional immunoassays used for routine monitoring estradiol; however, the threshold is still above the mean estradiol concentrations, as observed in the ALIQOUT study. An assay with a lower LLOQ or the option to extrapolate concentrations below the LLOQ would be better to adequately compare estradiol concentrations with the observations in the ALIQUOT study; however, these very sensitive assays are not routinely available.

Monitoring the concentration of the aromatase inhibitor itself as a pharmacokinetic marker is a more accessible method than using the concentration of estradiol as a pharmacodynamic marker. In cases where concentrations below the threshold are observed, a risk of inadequate estradiol suppression exists. Ideally, this risk should be confirmed by monitoring the concentration of estradiol.

During the first year after bariatric surgery, a substantial amount of variation exists in the pharmacokinetic profile of orally administered drugs.[12,13] Therefore, TDM should be repeated in the first year. The recommendations for dosing and monitoring anastrozole and letrozole are summarized in Table 2.

After bariatric surgery, the compatibility of the drug with postsurgery lifestyle and dietary recommendations, as well as with recommended concomitant drugs (eg, proton pump inhibitors, calcium, and vitamin D) must be considered. For example, smaller meal portions with a lower fat content are recommended after surgery.[34] Theoretically, the absorption of drugs that should be administered with food to ensure adequate absorption could be decreased due to these dietary recommendations. However, such reduction does not occur for tamoxifen, anastrozole, or letrozole. Considering drug–drug interactions, these drugs are also compatible with proton pump inhibitors (or other gastric acid suppressing agents), calcium, and vitamin D.

CONCLUSIONS

Our case series shows that higher initial doses of tamoxifen are required by patients after RYGB. For certain patients with an affected CYP2D6 allele, adequate endoxifen concentrations have not been achieved with a tamoxifen dose of 40 mg/d, suggesting that tamoxifen may not be a suitable treatment for these patients. In addition, because endoxifen requires approximately 3 months to reach steady-state conditions, we recommend performing genotyping before the initiation of tamoxifen therapy in this population; this is because approximately one-third of patients (those with a prevalence of IM and PM phenotypes) may not benefit from this therapy. For the aromatase inhibitors, letrozole, and anastrozole, adequate estradiol suppression was obtained with standard doses. However, because limited data are available on the disposition of these drugs in patients after RYGB, and due to substantial variation in the pharmacokinetic profile of orally administered drugs over time after bariatric surgery, we advise monitoring the plasma concentrations periodically during the first year after surgery for all oral antihormonal drugs. Of note, TDM of these agents may not be easily accessible everywhere, and no definitive exposure-efficacy relations have been established. However, until larger studies are available regarding the efficacy and safety of oral drugs in this specific population, TDM is the preferred approach to ensure efficacy for these patients.

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