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Bioavailability of vortioxetine after a Roux-en-Y gastric bypass

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The impact of bariatric surgery on depression appears to be positive during the early months (the so-called "honeymoon period"), but depressive symptoms tend to increase 36 months post-intervention (1). Despite the high prevalence of depression and obesity, little is known about pharmacokinetic modification of psychotropic drugs in patients undergoing bariatric surgery. Briefly, the reduction of gastric volume leads to a decrease in gastric mixing, an increase in gastric pH and an increase in gastric emptying, affecting disintegration and dissolution of the oral medication. The reduction in intestine length after Roux-en-Y gastric bypass (RYGB) leads to a reduction in the absorptive surface area and modification of presystemic drug metabolism (2). Limited clinical data are available for psychotropic drugs and concern mostly antidepressants. Two single-dose cross-sectional pharmacokinetic studies with 100 mg of sertraline and 60 mg duloxetine found a significant decrease in the area under the plasma concentration time curve compared to the placebo group (3, 4). A case series of four patients found a 33% (4%–71%) decrease of serum escitalopram concentrations compared to preoperative values two weeks after RYGB surgery (5). Another case series of 12 subjects treated with selective serotonin reuptake inhibitors (SSRI) and serotonin-noradrenaline reuptake inhibitors (SNRI) showed a decreased area under the curve (AUC) between 36 to 80% in eight patients 1 month after RYGB intervention (6).

We present here the case of a 24-year-old Caucasian woman with a history of class III obesity, type 2 diabetes, non-alcoholic fatty liver disease and anxiety-depressive disorder previously been unsuccessfully treated with two SSRIs (sertraline and fluoxetine). Vortioxetine, a “multimodal serotonin modulator" acting as an SSRI and additionally on 5-HT_{1A}, 5-HT_{1B}, 5-HT_3 and 5-HT_7 receptors, was introduced with good clinical efficacy on mood symptoms. The latter has a bioavailability of 75%, maximum plasma concentration reached 7–11 hours post-dose and an elimination half-life between 59 and 69 hours. It is metabolized extensively in the liver, mainly via cytochrome P450 enzyme (CYP) 2D6 and, to a lesser extent, via CYP3A4, CYP2C19 and CYP2C9 into six inactive metabolites (7). Additionally, she was treated with metformin (1000 mg/d), liraglutide (1.8 mg/d) and biotin (10 mg/d).

Following assessment by the bariatric multidisciplinary team, she was eligible for an RYGB intervention. During the preoperative period, two blood level measurements of vortioxetine at 200 and 126 days before the intervention were taken. All concentrations were determined in steady-state conditions (> 2 weeks at stable dosage before analysis) and after maximum plasma concentration (> 7 hours between last drug intake and blood sampling). All analyses were run using a UPLC-MS/MS (Waters Corporation, Milford, MA USA) method used for routine purposes. Vortioxetine concentrations were 24 and 23 ng/mL, using a daily dosage of 10 mg/d (Table 1).

She underwent a RYGB intervention without complications. Metformin, liraglutide and biotin treatments were stopped after the intervention. She continued to receive vortioxetine in liquid form at the same dosage of 10 mg per day during the first month. After this period, the liquid form was switched to tablets at the same dosage. Vortioxetine blood level measurements were performed at 91, 224 and 308 days postoperatively to evaluate possible malabsorption. Vortioxetine concentration dropped to 11 ng/mL 91 days after the intervention, using the same dosage. Based on this result and with the aim of avoiding a depressive relapse, the daily dosage was increased to 20 mg/d. After this dosage augmentation, vortioxetine concentration increased to 24 ng/mL at day 224 and 27 ng/mL at day 308, values

comparable to the preoperative period. Additionally, a phenotyping test was completed at day 308. A low-dose phenotyping cocktail approach was used to assess in vivo activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (8). Metabolic ratios (Table1) indicates an intermediate metabolizer phenotype for CYP2D6 and a normal phenotype for CYP2C19, CPY2C9 and CYP3A4.

The evolution of vortioxetine concentrations corrected by the daily dose (C/D) during the preoperative and postoperative periods is presented in Figure 1. As the time between the last drug intake and blood sampling ranges between 8 and 24 hours, an estimation of trough concentration at 24 hours was made using a mean half-life of 64 hours (C/D calculated 24 hours post-dose: dotted line in Figure 1). During the postoperative period, the mean of C/D values decreased by approximately 50% compared to the preoperative period, using either the uncorrected or 24-hour adjusted C/D. This is slightly higher than the 25%–46% decrease in escitalopram C/D 6 weeks after intervention, as reported in a prospective case series (5). Interestingly, the postoperative C/D ratio remained unchanged one year after intervention, suggesting a long-term absorption impairment. This is in contradiction with another prospective case series with various SSRIs and SNRIs which found a normalization of AUC/dose ratio after one year (6). However, two case-controlled studies investigating sertraline and duloxetine found a decrease of the AUC of approximately 60% compared with matched controls one year post-RYGB, also suggesting an impaired bioavailability during at least the first year (3, 4).

Of note, preoperative C/D values ranged between 2 and 2.5, two-fold higher than the reported C/D in the literature (mean value 1.1), but these decreased to normal values in the postoperative period (9). As the phenotyping test indicated an intermediate metabolizer phenotype for CYP2D6, we may hypothesize that the high pre-operative C/D values were due to impaired metabolism, compensated by a decrease in absorption during the postoperative period. Normal activity for CYP3A4, CYP2C19 and CYP2C9 were also observed; however these are minor metabolic pathways and probably did not compensate for the intermediate activity of CYP2D6. Of note, no co-medication known to inhibit or induce CYP activity was found in the medical record files for the pre- and post-operative periods. Regarding the validity of a phenotyping test in post-RYGB conditions, a recent cohort study using the same methodology found no significant influence from this intervention (10). Over-compliance during the preoperative period may also be a reason for the high C/D ratio. However, due to the long half-life, this over-compliance should last for several weeks before each blood sample.

Because mood symptoms are often changing during the first postoperative year, it is difficult to assess whether this is due to environmental/psychological factors rather than malabsorption of antidepressive treatment. For this reason, routine use of therapeutic drug monitoring (TDM) is a valuable tool to exclude mood relapses due to malabsorption. General recommendations regarding oral pharmacotherapy after bariatric surgery are often based on a modification of the formulation: orally dispersible, liquid, crushing pills if applicable, increasing / dividing the daily dose, or changing the psychotropic drug (2). Briefly, a psychopharmacotherapy adaptation should be initiated during the preoperative period based on a determination of the basal psychotropic drug concentration (if applicable) and to evaluate the possibility of switching to a liquid oral dosage or sublingual melting forms. Shortly after surgery, clinicians should be aware of the presence of withdrawal symptoms and plasma levels should be obtained to exclude malabsorption. In case of malabsorption, daily dosage increase, switching to liquid oral dosage forms,

crushing tablets (according to the package insert) or dividing the daily dosage into several daily drug intakes are strategies that can easily be implemented. All these strategies should be followed by TDM to assess their efficacy.

CONFLICTS OF INTEREST

FV received honoraria for conferences or teaching CME courses from Forum für Medizinische Fortbildung. CBE received honoraria for conferences or teaching CME courses from Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Mepha, Otsuka, Sandoz, Servier, Vifor-Pharma and Zeller in the past 3 years, and for writing a review article for the journal “Dialogues in clinical neurosciences” (Servier). All authors reported no potential conflict of interest in relation to the content of the present submission.

HUMAN AND ANIMAL RIGHTS

This article does not contain any studies with human participants or animals performed by any authors.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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Table 1: Clinical parameters before and after bariatric intervention.

Parameter	Preoperatively (days)		Postoperatively (days)		
	200	126	91	224	308
Therapeutic drug monitoring information					
Dose, mg/d	10	10	10	20	20
Time between last drug intake and blood sampling, h[#]	24	10	8	12	9
Serum concentration, ng/mL	24	23	11	24	27
Calculated serum concentration 24 hours post-dose, ng/mL	24	20	9	21	23
Clinical information					
Weight, kg	125	125	109	94	90
BMI, kg/m^2	43.8	43.8	38.2	32.9	21.5
Weight loss, %			13	25	28
Phenotyping results (CYP activity)					
CYP 1A2					Slow
CYP 2B6					Normal
CYP 2C9					Normal
CYP 2C19					Normal
CYP 2D6					Intermediate
CYP 3A4					Normal

Trough serum concentration at 24 hours post-dose has been calculated by using a mean half-life of 64 hours.

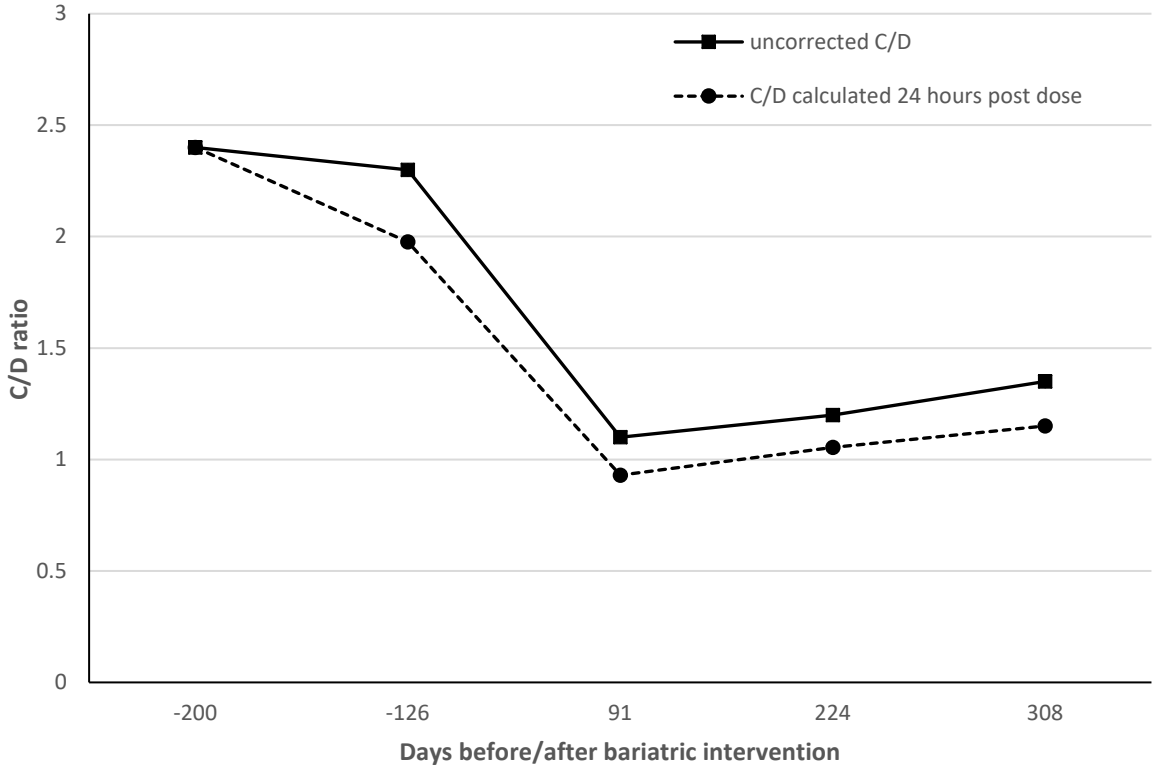

Figure 1: Concentration of vortioxetine corrected by the dose (C/D ratio) before (negative days) and after (positive days) bariatric surgery. The dotted line corresponds to the trough concentration normalized at 24 hours after last drug intake corrected by the dose.