Protocol

The BAR-MEDS study: Changes in Drug Pharmacokinetics After Bariatric Surgery – a Series of Prospective studies

COMMENT/COVER PAGE
The study includes pharmacokinetic measurements of a range of different drugs. For technical reasons, and as adviced from the ClinTrials-contact person at the university, the study was registered on ClinicalTrials.gov as separate, drug-specific entries. Consequently, this document pertains to the entries:

- **NCT03440190 (methylphenidate)**
- **NCT03460379 (escitalopram)**
- **NCT03460353 (dexamphetamine)**
- **NCT03460210 (atomoxetine)**
- **NCT03497169 (lisdexamphetamine)**
- **NCT03532477 (venlafaxine)**
- **NCT02904291 (amlodipine)**
- **NCT03538457 (paracetamol)**
- **NCT03535376 (valsartan)**
- **NCT03519893 (losartan)**
- **NCT03519906 (metoprolol)**
- **NCT03497143 (lamotrigine)**
- **NCT03497156 (lercanidipine)**
- **NCT03476525 (fluoxetine)**
- **NCT03476538 (gabapentin)**
- **NCT03476551 (hydrochlorothiazide)**
- **NCT03476603 (irbesartan)**
- **NCT03476577 (ibuprofen)**
- **NCT03449472 (quetiapine)**
- **NCT03460314 (buprenorphine)**
- **NCT03460327 (candesartan)**
- **NCT03460366 (enalapril)**
- **NCT03449485 (chlorprothixene)**
- **NCT03448783 (apixaban)**
- **NCT03440177 (ramipril)**

Since ClinicalTrials.gov in retrospect requires documents in English, the protocol was translated afterward using ChatGPT.

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Background

Each year, more than half a million obesity surgeries (bariatric procedures) are performed globally, with approximately three thousand of these at public hospitals in Norway. In Norway, surgeries are mainly divided into two procedures: gastric bypass and sleeve gastrectomy. Both are conducted to limit nutrient absorption.

However, the gastrointestinal tract also plays a crucial role in the absorption of orally administered drugs. 95% of patients referred for bariatric surgery are multimorbid, and a comparable data study indicated that patients referred for bariatric surgery use an average of 4.4 different medications. Medications for diabetes, depression, and hypertension are most common. These conditions may remit after surgery, but most patients still require some level of medication afterward.

The Bariatric Procedures

The surgeries are generally performed laparoscopically by experienced surgeons.

In gastric bypass, a portion of the stomach (cardia) is separated and transformed into a small pouch, approximately the size of an egg, and connected to part of the small intestine. The remaining stomach, duodenum, and about a meter of the small intestine are left behind, rendering them inactive in terms of absorption. Instead, food bypasses the stomach directly into a more distal section of the small intestine, only meeting gastric juices, bile, and pancreatic enzymes approximately one meter downstream. This setup creates both a restrictive and malabsorptive effect on the intestine.

Sleeve gastrectomy is a simpler procedure with no anastomosis (and thus reduced leakage risk). Around 80% of the stomach's outer curvature is removed, creating a tubular stomach (providing some restriction in intake) while preserving the pylorus (sphincter) and part of the antrum. Despite maintaining more normal anatomy, the physiological effects are likely greater than previously assumed, possibly due to significantly increased gastric emptying speed in the new stomach, even with the preserved pyloric sphincter.

Surgery and Bioavailability of Enteral Drugs

The gastrointestinal system significantly affects the bioavailability of oral drugs. Factors such as gastric pH and emptying rate, intestinal transit time, and first-pass metabolism due to mucosal enzymes can impact a drug's bioavailability. It is reasonable to expect that both gastric bypass and sleeve gastrectomy surgeries may influence several of these factors.

Changed bioavailability and pharmacokinetics of medications can have serious implications for patients, especially when a drug is essential or has a narrow therapeutic window. This issue has periodically been raised by bariatric surgeons, with the uncertainty around potential reductions in drug bioavailability sometimes used as an argument against surgical intervention for certain patients. In cases where surgery is reluctantly approved, sleeve gastrectomy has been preferred due to the assumption of lesser physiological impact (i.e., more normal anatomy).

However, bariatric surgery can also have the opposite effect on bioavailability. For drugs metabolized presystemically in the mucosa (stomach and/or intestines), the surgeries may

increase bioavailability. Examples include increased bioavailability of methadone after sleeve gastrectomy and ethanol following both sleeve gastrectomy and gastric bypass.

Only a limited number of drugs have been studied concerning the pharmacokinetic effects of bariatric surgeries. Most studies are small and have methodological weaknesses. The high number of bariatric surgeries, the fact that patients are typically multimorbid and use multiple medications, and our incomplete understanding of the surgeries' physiological effects underscore the need for more data. This document describes a project designed to investigate the pharmacokinetics of various drugs used by this patient population.

Study Objective

The purpose of the study is to map changes in the bioavailability of medications after undergoing sleeve gastrectomy and gastric bypass (among obesity patients). This includes examining bioavailability and pharmacokinetics in both the short and long term.

The primary endpoint will be bioavailability (AUC – 'area under the curve'), as a measure of the body's total exposure to the drug. Qualitative data such as Cmax (maximum drug concentration) and Tmax (time to reach Cmax) will also be included.

Study Design

The study will consist of a series of smaller studies, where each drug and each procedure define the individual study. Randomized crossover studies are not possible since the surgeries are irreversible; however, we will use the patients as their own controls, making the results more reliable with fewer participants needed.

The drugs relevant for study are those that the Department of Clinical Pharmacology has analytical methods for (see appendix). These include most psychopharmaceuticals, antiepileptics, analgesics, blood pressure medications, and a variety of other drugs.

Data Collection

Descriptive Data

- Gender, age, medical history, and medication use – collected from patient records.

Blood Samples

- Baseline blood tests for hemoglobin (Hb), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (GT), alkaline phosphatase (ALP), albumin, total bilirubin, international normalized ratio (INR), creatinine, C-reactive protein (CRP), and orosomucoid.
- Serum concentration of the drug as a basis for pharmacokinetic analysis.
- Blood sample for pharmacogenetic analysis of CYP enzymes and possibly other drug-metabolizing enzymes.
- Blood for biobank storage.

Additional Measurements

- Body composition analysis (bioelectrical impedance analysis) for distribution volume calculation.

Procedures

Participants arrive in the morning, either at the Research Unit or at the Center for Obesity Research at St. Olavs Hospital. Medication will be administered under observation by study personnel.

Participants must arrive fasting, meaning:

- Clear fluids can be consumed up to 2 hours before arrival.
- Coffee, grapefruit juice, and tobacco should be avoided from midnight the night before.
- One hour after medication administration, the participant is given a standardized meal, while subsequent meals are taken according to the participant's preference.

Sample collection procedures will depend on the drug's half-life. Drugs administered once, twice, or three times daily will each follow a specific sampling schedule, ensuring that the total blood volume drawn remains within safe limits. For example, a full 24-hour series for up to two drugs will involve a total of 89 ml, including discarded blood. For patients with three or more drugs, the blood volume will be doubled (178 ml). No more than this amount will be collected. By comparison, blood donors typically give 500 ml in one donation.

Administration Frequency	**Biobank**	**Initial Sample**	**0.5 hr**	**1 hr**	**1.5 hr**	**2 hr**	**2.5 hr**	**3 hr**	**3.5 hr**	**4 hr**	**6 hr**	**8 hr**	**12 hr**	**24 hr**	**Total Blood Volume (incl. discarded samples)**
Once a day	X	X	X	X	X	X	X	X	X	X	X	X	X	89 ml	
Twice a day	X	X	X	X	X	X	X	X	X	X	X			82 ml	
Three times a day	X	X	X	X	X	X	X	X	X	X				82 ml	

Sample Handling Samples are collected in 5 ml serum tubes without gel (red with black ring) at each sampling time point. If a venflon is used, 2-3 ml of blood is discarded before collection. Tubes are allowed to coagulate for 30 minutes before centrifugation at room temperature for 10 minutes at 2200xG. Serum is pipetted into Nunclon tubes (2 ml) and labeled with the relative sampling time. Samples are stored in a refrigerator until they are collectively sent to the Department of Clinical Pharmacology. If samples are collected on a weekend, they are stored in a refrigerator until the next weekday.

Blood samples for pharmacogenetic analysis are taken in EDTA tubes and sent directly to the relevant department, typically the Department of Medical Genetics at St. Olavs Hospital.

Additionally, two EDTA tubes and one serum tube are collected per test day for biobanking. The serum is divided into two Nunclon tubes, frozen, and registered in the BAR-MEDS biobank. Biobank1 is the data processor for the BAR-MEDS biobank, utilizing Biobank1's infrastructure (software, barcode labels) to achieve the same quality control as other Biobank1 projects. Unless designated otherwise by the clinic manager, the project leader will be responsible for the BAR-MEDS biobank.

Testing Schedule

Testing of serum drug concentration will occur at the following time points:

- Preoperative
- One week after surgery
- One month after surgery
- Six months after surgery
- One year after surgery

The first test can be conducted at any time prior to surgery, except immediately preoperatively if the patient is on a low-calorie diet. In addition to a baseline test, four postoperative test points are chosen. The rationale for several postoperative tests over time has multiple aspects. Shortly after surgery, the mucosa might be edematous, potentially affecting presystemic metabolism. Additionally, these patients enter a catabolic state and experience significant weight loss over the first year, which may indirectly affect drugs for which body mass determines the volume of distribution. Repeated postoperative tests will thus help indicate the physiological processes taking place in the body, such as whether bioavailability changes occur more quickly than can be attributed to distribution volume changes alone. Another reason for multiple tests is that patients will typically need adequate medication throughout this period. Finally, if there is a clear trend in pharmacokinetic changes across these tests, it may suggest that we have not yet reached a final and stable post-surgical effect by the one-year test.

Test Dose

The patient will take the prescribed drug as directed by their own physician. Participation in the study thus involves no changes to medication or prescription of new drugs.

Participant Selection

Inclusion Criteria

Group 1:
Patients with morbid obesity scheduled for gastric bypass at St. Olavs Hospital or Namsos Hospital.

Group 2:
Patients with morbid obesity scheduled for sleeve gastrectomy at St. Olavs Hospital or Namsos Hospital.

Exclusion Criteria

- Previous intestinal resection

- Lack of capacity to give informed consent

Sample Size

Bioequivalence studies follow a standard study design recommending at least 12 participants per group. Since the study comprises a series of individual drug studies (one study per drug per surgical technique), the hypothetical maximum number of participants could be: 12 participants x 2 surgical techniques x 109 drugs = 2,616 participants.

The actual number will be significantly lower, primarily because many patients are multimorbid and use several drugs simultaneously. In such cases, multiple drugs can be analyzed within the blood volume limits. Given that participants in the study use an average of 2.5 drugs within the study's analytical range (the average number of medications is 4.4), approximately 1,000 participants are expected. Each year, up to 100 patients in Trondheim and 200 in Namsos undergo the surgical techniques under study, with additional patients at the private Volvat Stokkan clinic. Considering the volume of bariatric surgeries is increasing, and that the study structure allows for a separate sub-study for each drug, this study is feasible.

Recruitment Procedure

The obesity clinic physicians lack the capacity to systematically review patients' medication lists for study inclusion. Therefore, a researcher affiliated with the Center for Obesity Research at St. Olavs Hospital will review referrals for patients undergoing bariatric surgery evaluation. The Center for Obesity Research, an entity within St. Olavs, is physically and organizationally integrated with the Obesity Clinic.

The researcher will note patients taking relevant medications, and the physician involved in the assessment will provide initial information about the study. Patients who express disinterest in participation or in learning more about the study will not be approached further. Other patients will be contacted by the researcher with more information about the study for potential inclusion.

For patients at Namsos Hospital and Volvat Stokkan, the same will occur in collaboration with a nurse or surgeon associated with the surgical operations, either through direct coordination or review of referrals. Referrals at St. Olavs Hospital and Namsos Hospital will be accessed via Doculive.

Research Environment

Collaborators and Research Team

Center for Obesity Research, St. Olavs Hospital. The study is led by the center, which is mandated to develop and evaluate treatment methods for obesity, focusing on patient-centered clinical research.

- Research Nurse Magnus Strømmen (Project Leader), St. Olavs Hospital
- Professor Bård Kulseng, St. Olavs Hospital
- Chief Physician Ronald Mårvik, St. Olavs Hospital

Department of Clinical Pharmacology, St. Olavs Hospital. The department is one of the country's leading facilities for analyzing drugs in biological materials and has extensive experience with various types of drug studies.

- Professor Olav Spigset (Medical Supervisor), St. Olavs Hospital
- Chief Physician Arne Helland, St. Olavs Hospital

Namsos Hospital has a large bariatric surgery practice. The clinic will actively contribute to recruiting study participants by identifying suitable candidates/medications during the assessment process.

- Chief Physician Hallvard Græslie, Namsos Hospital

Volvat Stokkan, Trondheim performs numerous sleeve gastrectomies. The clinic will actively contribute to recruiting study participants by identifying suitable candidates/medications during the assessment process.

- Coordinating Nurse Janicke Solberg

The Research Unit at St. Olavs Hospital, along with the Center for Obesity Research, can assist in the practical execution of the study.

Ethics and Safety

Safety Assessment

Aside from venous blood sampling, there are no interventions associated with project participation. The total volume of blood drawn is significantly less than what is considered safe in blood donation. A venous cannula (venflon) will be inserted to minimize the number of needle sticks for the participant. For participants who are difficult to cannulate, it may be necessary to allow them to leave the department for a few hours with the cannula in place. This could be relevant during 24-hour series where the participant sleeps at home. Participants will be well-informed about the risk of phlebitis and what actions to take if the cannula becomes dislodged.

Study participants are covered by Norwegian patient injury insurance, as specified in the Patient Injury Act §1.

Potential Benefits

Regardless of the outcome, the study may benefit participants as the results will provide insights into whether the participant has an adequate dosage of the measured drugs post-surgery. Upon completion of the last test, processed information will be shared with the participant through their general practitioner. If significant clinical changes are detected in essential medications early in the test series, the project's medical supervisor will assess whether the general practitioner should be notified at an earlier stage. Normally, these patients undergo surgery without any focus on appropriate postoperative medication dosing.

Results from the study will also benefit the patient groups as a whole once the information is published and made available. The findings will enable pharmacokinetic considerations for drugs to be integrated before choosing a surgical procedure, and will also increase attention on drug dosing in the postoperative phase. This can lead to health benefits for patients.

On a societal level, potential benefits lie in whether this study could help prevent long-term complications caused by medication use.

Ethics

We find the study ethically acceptable as it involves minimal risk while the potential benefits may have significant clinical value. Privacy will be safeguarded by de-identifying sample results, keeping the code key separate from data, and storing data on a project server at St. Olavs Hospital. In the information letter, participants will consent to data sharing with other researchers, aligning with the principles of data pooling and research transparency. Such sharing (of anonymized data) will occur only upon specific request and with project leader approval.

The study will be submitted for approval by the Regional Committee for Medical and Health Research Ethics (REK) and the Data Protection Officer for Research at St. Olavs Hospital.

Dissemination

We expect the study to generate a series of publications in international peer-reviewed journals. Preliminary and final findings will be presented at conferences. Additionally, findings will be integrated into education for both patients and healthcare professionals, with an emphasis on accessible scientific dissemination.

Timeline

This protocol essentially describes a series of parallel studies, where each drug tested represents a unique study group. Depending on the prevalence of the drug in the population, each group could consist of a single patient (for rare drugs) or up to twelve patients (for commonly used drugs).

The study is planned to run over a ten-year period. Since recruitment will occur in parallel with the clinic's patient evaluations, it is challenging to provide a precise forecast of progress. Should new analyses become available at the Department of Clinical Pharmacology, they may also be included in the study if relevant for the patient groups. The project itself is intended to continue for ten years.

Funding

The study has core funding from the Center for Obesity Research and the Department of Clinical Pharmacology but will seek additional funding. The most significant expenses will be the hiring of study nurses with experience in pharmacokinetic studies and training in Good Clinical Practice (GCP), as well as costs associated with drug analysis and enzyme genotyping.

References

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