The impact of bariatric surgery on the pharmacokinetics of drugs in patients with obesity

A protocol for a planned systematic review of the literature

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**Rationale**

Obesity is a growing global health problem. The prevalence of obesity in the industrialized world is at an all-time high (>20% in Norway, 36% in the USA)(1, 2), and obesity related comorbidities contribute significantly to the burden of disease.

Although lifestyle intervention and behavior modification programs are valid options for the treatment of obesity; bariatric surgery is the treatment modality that can give the best results for long-term weight reduction.

Drugs are frequently used for the treatment of various obesity-related comorbidities such as type 2 diabetes mellitus, hypertension and dyslipidemia. It is known that weight loss is a key component in the treatment of these co-morbidities. Caloric restriction and a healthy diet may improve insulin sensitivity, glucose tolerance and high blood pressure.

Roux-en-y gastric bypass is the method of choice, and its effects are thought to go beyond weight reduction. There is evidence of beneficial effect from the procedure on glucose metabolism, independent of weight loss. Additional effects may be present due to the changes in macronutrient content, microbiota as well as changes in physiology after surgical modification of the upper GI-tract.

There are several bariatric surgery techniques in use. In general, most of them reduce the volume of the gastric ventricle, and/or the absorptive surface are in the intestine(3), bypassing part of the small gut.

Bariatric surgery may hence have an effect on the bioavailability of many drugs (4). It is recently shown, for instance, that the bioavailability of atorvastatin is increased just months after biliopancreatic diversion with duodenal switch and gastric bypass (5). The effect can be hypothesized to be mainly due to the bypass of most metabolic active sites of the small gut. But the reduced absorptive surface area, and its possibly opposing effect to the absorption, must be considered. Additionally, there is little certainty of whether this change in bioavailability can be affected by weight loss alone. Various proteins also affect the bioavailability of drugs in humans, and the concept of the first-pass-metabolism of drugs in both the gut and the liver, is well known. These metabolizing enzymes, to a variable extent, restrict the bioavailability of drugs.

There is a large variability, both within and between individuals, in the uptake and elimination of drugs. Bioavailability is therefore to a large degree dependent on genetic, environmental and disease related factors. Data in the literature may indicate significant relations between obesity (BMI), the expression and exposure to above mentioned factors, changes related to bariatric surgery and the bioavailability of drugs.

We believe that it is of major interest to do a systematic review of the literature regarding the bioavailability of drugs in patients with obesity, and the effects of surgical weight loss on the different factors affecting the bioavailability. It will also be important to include and review the effect of weight and weight loss on factors associated with bioavailability.

**Objective**

The purpose of our review is to describe the current literature systematically, basing our methods on the PRISMA-statement(6, 7). We will not perform data-extraction and a meta-analysis.
The objective is to find pharmacokinetic studies on patients with obesity, before and after bariatric surgery. We shall assess change in the bioavailability of drugs following surgery.

**Eligibility criteria**
Studies included will be selected according to the criteria outlined below.

**Design**
We will include pharmacokinetic randomized controlled trials (RCTs), controlled (non-randomized) clinical trials (CCTs), controlled before-after studies, prospective and retrospective comparative cohort studies and case-control studies. Both single and cocktail drug probing will be accepted. Only studies on orally administered drugs will be included. Studies on intravenously administered drug pharmacokinetics will only be included if the purpose is to compare this with oral pharmacokinetics in patients with obesity.

Case series and case reports will be excluded. Studies involving gas anaesthetics will be excluded.

**Participants**
We will include studies examining adult humans (18 years or older) with obesity (BMI ≥30) as well as studies comparing these patients to normal weight adults. Concomitant drug therapy will not be an exclusion criterion unless this can interfere with drug probes.

**Interventions**
All bariatric surgical interventions will be of interest. Studies on the effect of dietary/lifestyle-modification based weight loss on bioavailability will also be included.

**Outcomes**
Endpoints concerning bioavailability of drugs are of primary interest.

**Timing**
Studies with both short-term and long-term follow up, of any length, will be included.

**Setting**
There will be no restrictions by type of setting.

**Language**
Only articles reported in English will be included. A list of possibly relevant titles in other languages will be provided as an appendix.

**Publication status**
Original articles published ahead electronically, ahead-of-print, will be included. There will be no restriction on publication dates. Conference abstracts, not leading to publication, will be excluded.

**Information sources**
Literature search strategies will be developed, in cooperation with health science librarians, using medical subject headings (MeSH) and text words related to pharmacokinetics, bioavailability, bariatric surgery and weight loss. We will search MEDLINE, EMBASE, as well as the Cochrane Central Register of Controlled Trials. The electronic database search will be supplemented by searching for
trial protocols through ClinicalTrials.gov, to find ongoing studies on the subject matter. The literature search will be restricted to English language and human subjects.

**Search strategy**
The search strategy in the Ovid interface will be attached in an appendix, and will be created by a Health Sciences Librarian with expertise in systematic review searching. This will then be modified further by input from the review project team. The search strategy will then be peer reviewed by a second librarian.

A draft search strategy is included in this protocol.

**Study records**
Literature search results will be uploaded to www.covidence.org, an Internet based review program that facilitates review literature screening and collaboration among reviewers.

The team will develop and test screening questions based on the inclusion and exclusion criteria. Citation abstracts and full text articles will be uploaded.

Prior to the formal screening process, a test exercise will be undertaken to analyse and refine the screening questions.

**Selection process**
Two members of the review team (Angeles, Robertsen) will independently screen the titles and abstracts yielded by the search against the inclusion criteria. One senior team member will resolve conflicts (Hjelmesæth).

Full reports for all titles meeting the inclusion criteria will be obtained, and a final inclusion process will be done by the above mentioned members of the team in concert. Reviewers will resolve uncertainty and disagreement by discussion. Study authors may also be contacted if this is required to resolve any uncertainty.

**Data items**
Data items for variables concerning obesity, surgical treatment and pharmacokinetics will be described but not extracted as data synthesis and a meta-analysis is out of the scope of this review.

**Outcomes**
Anthropometric results at baseline and after intervention will be sought for, along with pharmacokinetic measures affecting bioavailability. These measures will include BMI, waist and hip circumference, as well as body composition analysis. The pharmacokinetic measures comprise parameters concerning bioavailability, including: $C_{\text{max}}$, $T_{\text{max}}$, area under the curve (AUC), and also activity and expression of drug-metabolizing proteins (CYP450, P-gp, OATPB1).

**Timeline**
The entire process of screening, reviewing and composing a review article is planned to be completed by the end of 2016.

**Financing**
The review will be conducted as a part of the COCKTAIL-study (ClinicalTrials.gov).
NCT02386917), a collaboration between the Morbid Obesity Centre at Vestfold Hospital Trust in Norway, Astra-Zeneca R&D (Gothenburg, Sweden), and the School of Pharmacy at the University of Oslo. Funding is provided to the authors by their respective institutions. The authors are all investigators and participants in the COCKTAIL-study.

Appendix 1
Search design

Appendix 2
Inclusion/exclusion criteria of articles included in the search

References