

## **Study Protocol**

**Title: The Need of Dosing Adjustment for Simvastatin in Obese Patients post Bariatric Surgery-  
Laparoscopic sleeve gastrectomy (LSG)**

## **Abstract**

Morbid obesity (Body mass index > 40 kg/m<sup>2</sup> or 35-39 kg/m<sup>2</sup> with comorbidity; 37.5 kg/m<sup>2</sup> for Asians) is a growing global health issue. Bariatric surgery is the only intervention that has demonstrated sustainable reduction in weight and comorbidities.<sup>1,2</sup> Among the various bariatric procedures, laparoscopic sleeve gastrectomy (LSG) has rapidly gained popularity worldwide.<sup>3,4</sup> Physiological alterations following LSG include reduction in gastrointestinal surface and reduced retention of food. Bioavailability of drugs may be affected but published literature in this area is sparse and studies are usually small and uncontrolled.<sup>5-7</sup> Moreover, some reports concerning gastric banding and jejunoileal bypass are no longer practiced because of the associated risk. In general, bioavailability of orally administered drug changes with a reduction in gastrointestinal area. While Kroll et al showed slight increase in area under curve of rivaroxaban post bariatric surgery<sup>8</sup>, Skottheim et al demonstrated significant but variable change in systemic exposure of atorvastatin after gastric bypass (from threefold decrease to twofold increase) that diminished but was sustained with time (21-45 months post gastric bypass)<sup>9-10</sup>.

No study has investigated the change in pharmacokinetics of simvastatin post LSG.

Simvastatin is a widely-used lipid-lowering agent with a low bioavailability of 5% due to the extensive first pass metabolism.<sup>11</sup> As simvastatin undergoes hydrolysis in the stomach to the active form<sup>12</sup>, it is postulated that bioavailability of simvastatin will decrease after LSG.<sup>13-15</sup> A decrease in bioavailability may be associated with reduced efficacy. Authors of review articles suggested choosing an alternative agent to simvastatin post bariatric surgery. However, such recommendation is largely based on theoretical concern rather than solid evidence.<sup>14,15</sup> A previous study attempted to model the pharmacokinetics of simvastatin post Roux-en-Y and biliopancreatic diversion with duodenal switch.<sup>13</sup> The data is not applicable to LSG and the model did not take into account of the pH-dependent hydrolysis. This will be the first study aiming to investigate the change in systemic exposure of simvastatin post LSG.

## **Aims & Objectives**

The aim of the study is to investigate the effect of laparoscopic sleeve gastrectomy on the pharmacokinetics of simvastatin.

## **Study design**

Study design: prospective, open, non-randomized, controlled, single-centre study

The study will be conducted with the approval from the Institutional Ethics and Research Board.

Participants: 10 patients undergoing sleeve gastrectomy

## Study Procedure

- Patient recruitment
  - o Subject selection:
    - Inclusion criteria:
      - Planned for laparoscopic sleeve gastrectomy at National University Hospital
      - Taking simvastatin
      - Aged 21 or above
    - Exclusion criteria:
      - Patient on concomitant treatment with medications/ food/ herbal supplements that may affect the pharmacokinetics of simvastatin: boceprevir, conivaptan, cyclosporine, efavirenz, mitotane, tocilizumab, rifamycin, amiodarone, amlodipine, aprepitant, azithromycin, colchicine, fenofibrate, imatinib, raltegravir, ranolazine, teriflunomide, ticagrelor, fusidic acid, protease inhibitors, telaprevir, telithromycin, gemfibrozil, erythromycin, clarithromycin, carbamazepine, rifampicin, ketoconazole, fluconazole, itraconazole, voriconazole, diltiazem, verapamil, dexamethasone, prednisolone, phenytoin, ritonavir, indinavir, nelfinavir, bosentan, telithromycin, nefazodone, St John's wort, orlistat, sibutramine and other strong CYP 3A4 inhibitors/ inducers
      - Pregnant ladies
  - o All patients referred to the National University Hospital for laparoscopic sleeve gastrectomy will be screened for inclusion into the study. Potential subjects will be screened and assessed at the Bariatric Surgery Clinic. Written consent will be taken at the Clinic. ( See Patient consent form) The potential subject's permission to be referred into a study will be obtained by the attending healthcare professionals prior to direct contact by any member of the research team, and the subject's agreement will be documented. The study aims to recruit 10 patients.
  - o Patients will be asked to stop taking simvastatin 5 days before the day of the study. Fasting is not required. Patients will also be informed that they will obtain SGD \$100 after completing the study as a token of appreciation and to compensate their time and inconvenience (if the study subject fails to complete the study, compensation will be pro-rated and paid out as \$50 per each blood sampling session).
  - Training
    - o Study members, namely Elaine Lo, Subashini Gunasegaran, Yeoh Siang Fei, will be trained for the following: 1) Explaining procedure of the study to recruited study subjects after informed consent is taken; 2) Delivering blood sample from the bariatric clinic to the lab for storage and 3) Procedures for compensating the patient after the study
    - o Nurses of the bariatric clinic will be trained to administer the study according to the study protocol: 1) Making sure study subject is suitable for blood sampling e.g. has stopped simvastatin for 5 days, vitals stable, IV plug properly set by physician; 2) Monitoring self-administration of simvastatin by the patient; 3) Drawing blood according to the pre-set time points; 4) Monitoring patient for vitals and comfort after blood draw; 5) Documentation of details of blood sampling on the "Record for Blood Sampling"
    - o The training details (i.e. date, name of trainee and trainer, contents of training) will be recorded. Training records will be kept for 3 years after completion of the study.
  - Pre-bariatric surgery

- Recruited subjects will come to the clinic at 8:30am on the day of study. Blood taking will start at 9:30am. Fasting is not required.
- Nurses at the Bariatric Surgery Clinic will set an IV plug for blood sampling. They will also confirm with the subjects that simvastatin has been stopped for 5 days. Nurses will also check that patient has not been taking the interacting drugs in the past 5 days. The subject will take simvastatin 20mg at 9:30am (0 h). 5 mL of blood will be sampled at 0 h, 1 h, 2 h, 3 h, 5 h, 7 h. Blood sample will be taken in EDTA tubes and kept in ice. (See Record of blood sampling). Study subjects will be staying at the Bariatric Surgery Clinic and monitored by nurses who are trained for care and monitoring of patients with IV cannulation.
- All the blood samples will be transferred to the lab in ice after the last blood sample is drawn at 7 h. Blood samples will be spun down and frozen.
- Surgical procedure
  - Laparoscopic sleeve gastrectomy (LSG) is performed for most patients requiring bariatric surgery at the National University Hospital. This is a restrictive procedure where the stomach is tubularized and the excess part is removed. About 75% of the stomach will be removed in this way.
- Post-bariatric surgery
  - Patients will be invited to return to the clinic for another blood sampling session after 3 months. If the patient takes proton pump inhibitor prior to the study, the same dose should be maintained at 3 months when the patient returns for the study.
  - The blood sampling procedure for pre-bariatric surgery will be repeated.
  - \$100 will be given to patient upon completion of the second blood sampling session.

#### Blood sample analysis

- Liquid chromatography–mass spectrometry (LC-MS) will be run when samples for all the patients (10) are collected.

#### Statistical Analysis

- Pharmacokinetic parameters (Area under curve, half life, Tmax and Cmax) of simvastatin and simvastatin acid before and after bariatric surgery will be calculated for each subject using pharmacokinetics software. (See Pharmacokinetics Evaluation Form) Each patient will serve as their own control and pharmacokinetic parameters before and after LSG will be compared with appropriate statistical tests (student t-test if parametric, mann-whitney u test if non-parametric).



## References

1. Santry, Heena P., Daniel L. Gillen, and Diane S. Lauderdale. "Trends in bariatric surgical procedures." *Jama* 294.15 (2005): 1909-1917.
2. Sjöström, Lars, et al. "Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery." *New England Journal of Medicine* 351.26 (2004): 2683-2693.
3. Ponce, Jaime, et al. "American Society for Metabolic and Bariatric Surgery estimation of bariatric surgery procedures in 2015 and surgeon workforce in the United States." *Surgery for Obesity and Related Diseases* 12.9 (2016): 1637-1639.
4. Buchwald, Henry, and Danette M. Oien. "Metabolic/bariatric surgery worldwide 2011." *Obesity surgery* 23.4 (2013): 427-436.
5. Backes, Charline Fernanda, et al. "Medication and nutritional supplement use before and after bariatric surgery." *Sao Paulo Medical Journal* 134.6 (2016): 491-500.
6. Yska, Jan Peter, et al. "Influence of bariatric surgery on the use and pharmacokinetics of some major drug classes." *Obesity surgery* 23.6 (2013): 819-825.
7. O'Kane, Mary, et al. "Guidelines for the follow-up of patients undergoing bariatric surgery." *Clinical obesity* 6.3 (2016): 210-224.
8. Kröll, Dino, et al. "Pharmacokinetics and pharmacodynamics of single doses of rivaroxaban in obese patients prior to and after bariatric surgery." *British Journal of Clinical Pharmacology* (2017).
9. Skottheim, I. B., et al. "Significantly altered systemic exposure to atorvastatin acid following gastric bypass surgery in morbidly obese patients." *Clinical pharmacology and therapeutics* 86.3 (2009): 311.
10. Jakobsen, Gunn Signe, et al. "Long-term effects of gastric bypass and duodenal switch on systemic exposure of atorvastatin." *Surgical endoscopy* 27.6 (2013): 2094-2101.
11. Lexi-comp online. <http://online.lexi.com/action/home>. Accessed on 20th March, 2017.
12. Vickers, S., et al. "Metabolic disposition studies on simvastatin, a cholesterol-lowering prodrug." *Drug Metabolism and Disposition* 18.2 (1990): 138-145.
13. Darwich, Adam S., et al. "A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution." *Journal of Pharmacy and Pharmacology* 64.7 (2012): 1008-1024.
14. Miller, April D., and Kelly M. Smith. "Medication and nutrient administration considerations after bariatric surgery." *American Journal of Health-System Pharmacy* 63.19 (2006): 1852-1857.
15. Snow, Vincenza, et al. "Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians." *Annals of internal medicine* 142.7 (2005): 525-531.
16. Edwards, Allan, and Mary HH Ensom. "Pharmacokinetic effects of bariatric surgery." *Annals of Pharmacotherapy* 46.1 (2012): 130-136.