

The New Weight Loss/Diabetes Drugs: Commercial Oversight, and Anesthesia Risks

Paul M. Kempen, M.D., Ph.D.

Television viewers cannot avoid the up-beat musical advertisements for glucagon-like peptide-1 receptor agonists (GLP-1) appearing as often as three to five times per hour on some channels. The ads suggest that these drugs are harmless, useful, and very desirable to help lose weight. Recently, advertisements have been promoting referral agencies for treatment, as these expensive drugs are difficult to acquire and produce large profits to manufacturers.

There is no accompanying notice that GLP-1 agents cause, by either central or peripheral mechanisms, significant gastric stasis or gastroparesis. There has been no mention of the significant anesthesia risks from this effect in these advertisements or even in the official Food and Drug Administration (FDA)-approved package inserts. Many drugs have historically received very strong notice including “Black Box Warnings” once anesthesia dangers are recognized. Anticoagulants are one such example.

While the anesthetic complications from the gastroparetic effects of GLP-1-class drugs are increasingly documented in the anesthesia literature,¹ prescribers and patients remain unaware of these dangers, even as the number of agents and patients is increasing rapidly. It is time pharmaceutical producers and the FDA provide this necessary information to protect patients.

GLP-1 agonist medications and dosing currently available on the U.S. market include:

- Dulaglutide (Trulicity®) **Once a week.**
- Exenatide (Byetta®) **Twice a day.**
- Exenatide extended release (Bydureon®) **Once a week.**
- Liraglutide (Victoza®) **Daily.**
- Lixisenatide (Adlyzin®) **Daily.**
- Semaglutide injection (Ozempic®, Wegovy®) **Once a week.**
- Semaglutide tablets (Rybelsus®) **Daily.**

Dual GLP-1/gastric inhibitory polypeptide (GIP) receptor agonist:
Tirzepatide (Mounjaro®) **Once a week.**

Table 1. Currently available GLP-1 receptor agonists

Recent direct contact with the FDA revealed that no appropriate action or notice is anticipated at this time to inform the public, pharmacists, and non-anesthesia prescribers. Pharmaceutical producers are unlikely to spontaneously provide adverse information regarding their newest multibillion-dollar products. The response to my call surprisingly documented that “the FDA has no authority over TV advertisements per se” and is only interested in adverse report collection at this time.

From many decades of clinical experience, I learned that notifications to the FDA of individual complications, which are currently simply attributed to anesthesia care, are quite

spotty and unlikely. The FDA’s failure to require publication of any warning or notice of the anesthetic dangers of these GLP-1 class drugs in the FDA-approved package insert, despite increasing identification and publication within the anesthesia specialty, is in my opinion negligent. It is imperative to provide binding notice to ALL medical personnel, including all primary-care prescribers, via these package inserts, over which the FDA does have authority, especially as manufacturers have large disincentives to declare this drug problem. Medical-legal recourse after individual serial complications will take years and typically targets only anesthesia practitioners, who are accused of malpractice.

The package insert currently states relevant information without reference anywhere to anesthesia:

Excerpts from Wegovy® (semaglutide) injection 2.4 mg FDA package insert

12.1 Mechanism of Action

GLP-1 is a physiological regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies show that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake. Drug interactions: Semaglutide delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution.

12.2 Pharmacodynamics

Semaglutide lowers body weight with greater fat mass loss than lean mass loss. Semaglutide decreases calorie intake. The effects are likely mediated by affecting appetite.

Gastric Emptying

Semaglutide delays gastric emptying.

12.3 Pharmacokinetics

With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 to 7 weeks after the last dose of 2.4 mg.

Figure 1. Wegovy package insert

Mandating public notice is also needed to protect patients using these very expensive GLP-1 agents, particularly as the individual prescribing these drugs is often unaware of anticipated surgical interventions. Having an empty stomach is paramount for safe anesthesia, including procedures under “sedation” in any and all elective situations.

Anesthesia suppresses the reflexes protecting against stomach content entering the lungs (aspiration) and causing pneumonia and even death. An empty stomach is thus so essential to safely proceed in elective care that typically elective procedures are cancelled as anesthetic routine if patients eat within six hours prior. In emergency situations, where stomachs do contain food, anesthetics require very specific management

and obligatory endotracheal intubation (EI) to protect patients against food aspiration. Many patients currently undergo elective anesthesia daily in the U.S. without EI. Use of EI typically requires deeper anesthesia, entails specific risks, and always prolongs the procedure's overall duration, creating problematic delays, especially in rapid turnover situations. Changing historical practice patterns and expectations is invariably difficult, limiting the introduction of new safety measures.

Patients using GLP-1 agents are experiencing aspiration resulting in hospitalizations including intensive care.¹ This has led to suggestions in specialty literature that preoperative ultrasound examination may be useful and necessary in GLP-1 patients to assess whether to proceed or cancel elective anesthesia.¹ The FDA has yet to take notice and implement or require needed warnings.

Ultrasound examination of the stomach is not routinely available, is typically done best by radiologists, and may be difficult because of interposed fat and bowel gas. Anesthesia personnel are not generally proficient at this evaluation and referral to radiologists incurs much more time delay and financial costs. Patients taking GLP-1 agonists are typically obese.

Anesthetizing obese patients has long been known to be associated with increased overall anesthetic risks, without the additional risks introduced by GLP-1 agents and associated increased stomach content volumes. Obese patients frequently complain of gastro-esophageal reflux disease (GERD), further facilitating aspiration. GERD may also give rise to concerns of long-term esophageal inflammation exacerbated by GLP-1 use, potentially facilitating esophageal cancer development. The drug's weight-loss effect includes the drug's ability to centrally create the feeling of fullness and lack of hunger for long periods of time, but also to keep the stomach from emptying normally. Often meal residue is detectable in the stomach for days, even after 24-hour starvation periods, as I have personally noted during gastroscopy. These drugs are often injected once a week.

The increasing number of patient complications has led the American Society of Anesthesiologists to produce the following guideline: "For patients on daily dosing consider holding GLP-1 agonists on the day of the procedure/surgery. For patients on weekly dosing, consider holding GLP-1 agonists a week prior to the day of the procedure/surgery. If the patient has no GI symptoms, and the GLP-1 agonists have been held as advised, proceed as usual."²

Guidelines are created with regard to business aspects of care: They must be "workable" as a consensus measure. They typically identify real problems.

I have personally been actively sampling for stomach contents in patients receiving GLP-1 agonists by placing Salem sump tubes and aspirating contents. I do find food products in their stomachs after 24-hours starvation and after one week from the last known dose. This guideline suggesting a 7-day interval from last dose is clearly a response to illuminate a real problem. However, the typical weekly 2.4 mg semaglutide dose, according to the package insert, takes five to seven weeks to be eliminated. Thus, at one week, the drug is expected to be present and working!

From my viewpoint as a physician overseeing the care of these patients, always placing an endotracheal tube for any

anesthetic appears prudent, given the drug's long persistence for months after injection. The unknown duration of gastric stasis in this "new" class of drug, especially when the only indication for using it is for elective weight loss, would make an interruption for 2 months reasonable and unproblematic. With the significant numbers of alternate drugs available to treat diabetes, it would be quite reasonable to extend the preoperative period of interruption to such long intervals as well, *when prescribed only* for diabetes management. Transitioning to alternate drugs when high-risk therapy has been identified is commonly practiced for many anticoagulants peri-operatively for planned procedures, especially if such identified risks will lead to interruption of a therapy. Such decisions must be made with patients informed of risks, which currently is not routine.

For example, long-acting insulin (glargine, ultralente) may be discontinued prior to surgery; glucose levels are instead stabilized by a combination of intermediate insulin (NPH) with short-acting insulin twice daily or regular insulin before meals and intermediate-acting insulin at bedtime. Perioperative diabetic dose adjustments typically reduce all insulins by 50 percent to prevent the very significant dangers of hypoglycemia, while accepting hyperglycemia as something to be acutely compensated. Insulin pumps are also removed for surgical procedures longer than one hour unless anesthetic personnel can change or stop the doses while frequent glucose level checks insure safety against hypoglycemia. Currently, metformin is also typically discontinued for surgeries and simple radiologic procedures, due to renal function complications that may arise. Oral agents are also generally held on the day of surgery until postoperatively as a routine measure. Regarding diabetic management, ongoing therapy is often complemented with insulin in many type II patients to control hyperglycemia pre- and preoperatively, which often is found to become uncontrolled due to surgical stresses and the paramount avoidance of hypoglycemia.³

Switching to oral daily GLP-1 medications has yet to be adequately studied as an alternative to the long-acting injectables. Often patients are uncertain of the time of their last dose, and as discontinuance is clearly needed, switching to other therapies early will contribute to overall improved perioperative diabetic management.

Production pressures become extreme in the shortest out-patient procedures such as colonoscopy, where EI is least likely to occur. EI itself has additional specific risks, especially in the increasingly complicated, infirm geriatric patients. Stopping these drugs early has significant advantages overall. One-week intervals are definitively not supported by current science or pharmacology principles.

At a bare minimum, given the increasing frequency of elective procedures in the U.S., inclusion of the known dangers regarding anesthesia should be mandated in the FDA inserts and all television advertisements, to increase awareness by patients and all prescribers. For a new drug with only recently recognized complications, any recommendation should err on the side of patient safety.

Metoclopramide may be useful to combat GLP-1 gastroparesis, but without specific studies its utility remains speculative, especially with frequent perioperative opiate administration.

A recent retrospective chart review of emergent procedures failed to find a higher risk of postoperative respiratory complications in patients using GLP-1 receptor agonists preoperatively, but recommended further study: "Given increasing use of GLP-1 RAs, larger-scale evaluations of their perioperative risks are needed; however, a randomized trial of preoperative GLP-1 RA withholding may not be feasible."⁴ While airway protection is always paramount in the emergency surgical procedures reviewed here and because airway complications are known to occur at increased rates five times that of elective surgeries,⁵ this study most strongly suggests a specific risk from intubation itself, best avoided in elective situations, rather than specifically from GLP-1 agonists. Thus, this information provides little reassurance to the vastly greater numbers of elective patients cared for daily, where the exceptional airway protections of emergency care are avoided.

Aspiration occurring in elective patients increases mortality nine-fold within 30 days.⁵ Elective procedures are facilitated by limiting dangers of intubation by protection based on adequate fasting, facilitating safer, less intrusive and rapid anesthetic care without these rapid-sequence intubations typical of emergencies. Very low level of airway complications, near 0.14%, are found in elective colonoscopies under anesthesia.⁶

Multiple case reports are appearing to document long-lasting effects of gastroparesis from GLP-1 agents, lasting up to weeks, thus documenting the problem as a real issue currently endangering patients who undergo elective procedures according to current guideline without the benefit of airway intubation and despite normal preoperative fasting intervals.⁷⁻⁹ Until such time as overall safety can be defined and ensured in the face of the rapidly increasing use of these expensive GLP-1 agents, prescribers and users must exercise great caution and vigilance.

Paul M. Kempen, M.D., Ph.D., is an anesthesiologist practicing in Weirton, W.V., and a past president of AAPS. Contact kmpnpm@yahoo.com.

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