Miracle Drugs, Hidden Dangers? Effects of GLP-1 Agonists on the Obese Patient

New Jersey Association of Nurse Anesthetists

Fall 2023 Meeting

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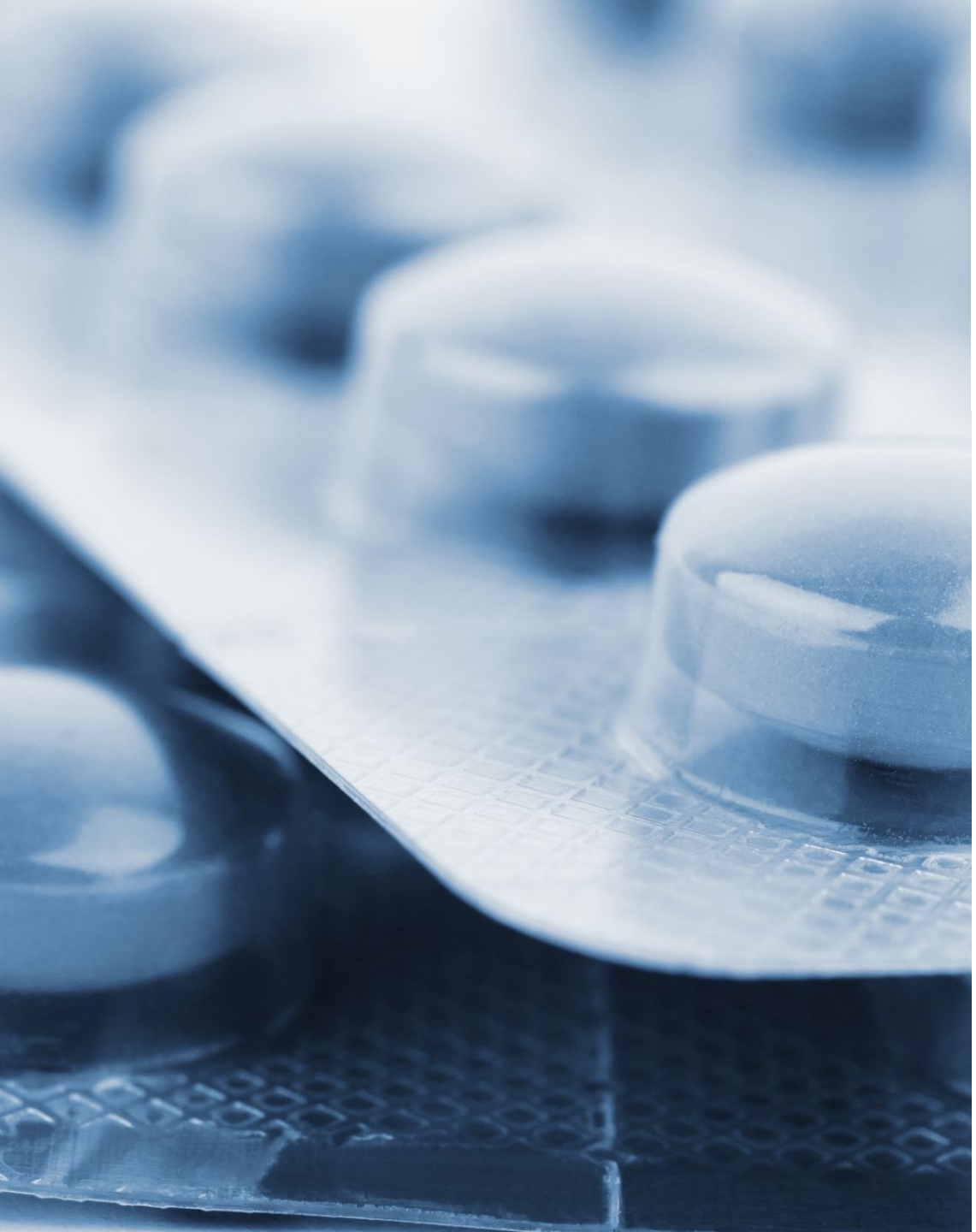


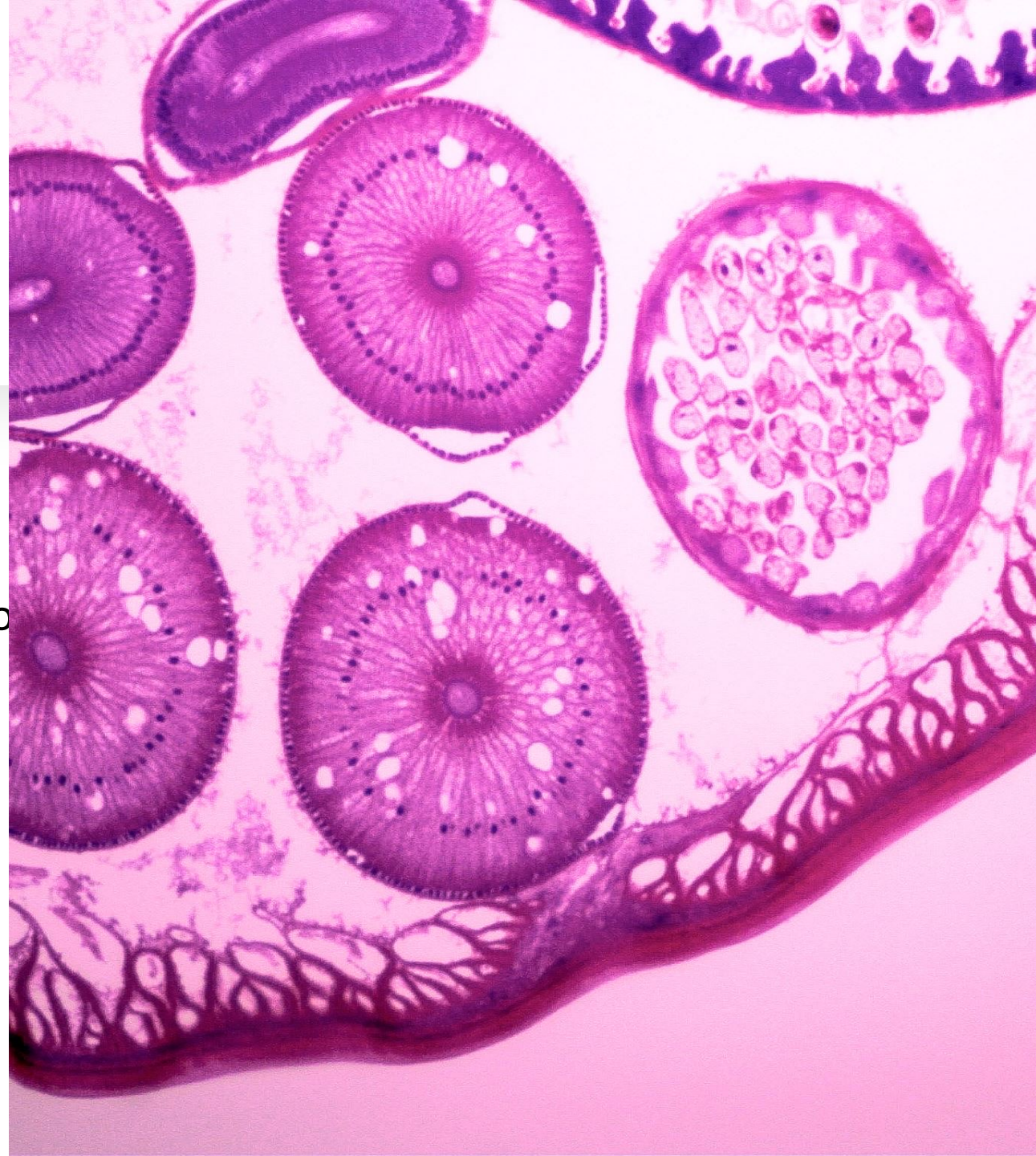
Objectives

By the end of the presentation, the anesthesia provider will be able to:

1. Understand the mechanism of action of the GLP-1 agonists in Type II diabetes and obesity.
2. Discuss the physiological alterations and side effects of this class of drugs.
3. Cite and resource current clinical studies on this topic.

Mechanism of Action and Effects

- GLP-1 synthesized by L cells in distal small bowel and nucleus tractus solitarius (NTS) in caudal brainstem
- GLP-1 agonists mimic incretin hormone GLP-1 that prompts pancreas to produce more insulin after meals
  - Keep food in the stomach longer so that patients feel full sooner, reduce liver's ability to make glucose, and suppress the appetite
- Effects on satiety through central and peripheral actions
- Distension of stomach results in production of satiation signals when gastric mechano-receptors are activated → these signals relayed to brainstem via vagus nerve
- Delays gastric emptying and gut motility
- GLP-1 affects gastric accommodation → change in gastric volume in anticipation of ingestion of food



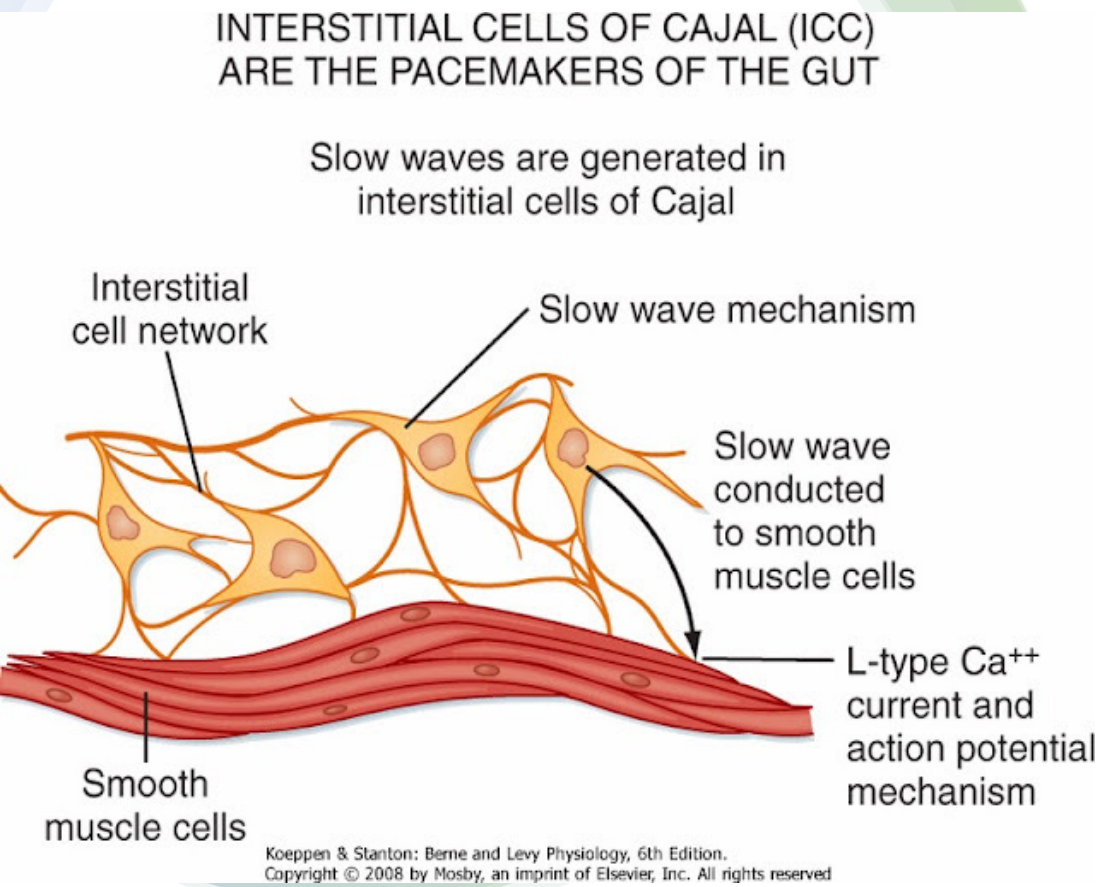
Physiological Alterations/Side Effects

Delayed gastric emptying thought to be result of GLP-1's effect on relaxation of proximal stomach in combination with an increase in tone of antropyloric region

In contrast, it accelerates colonic transit → thought to be mediated by parasympathetic nervous system

Vagal cholinergic input maintains gastric tone and presence of GLP-1 blunts postprandial pancreatic polypeptide release

Gastroparesis



- Diabetic gastroparesis multifactorial due to effects on vagus nerve, meyenteric plexus, impairment of inhibitory nitric-oxide-containing nerves, underlying smooth muscle dysfunction, and impairment of pacemaker interstitial cells of Cajal
- Presence of GI symptoms (N/V, diarrhea, abdominal cramps) as a guideline of whether to proceed may not be enough of a metric in DM pts as neuropathy also affects the afferent sensory nerve fibers
  - DM pts have poor correlation between presence of symptoms and presence of delayed gastric emptying

Evolution of GLP-I Agonists

Medications: Liraglutide (Victoza, Saxenda)

- Once daily SQ injection
- Dosages for weight loss are higher than doses previously studied in DM pts
- Higher doses (2.4 to 3 mg) are associated with increased rates of nausea and vomiting; max dose for DM 1.8 mg
- Half life ~ 13 hours
- No tachyphylaxis with respect to delayed gastric emptying
- At risk for delayed gastric emptying the entire duration of use of short acting formulations

Medications: Semaglutide (Ozempic, Rybelsus, Wegovy)

Once Weekly SQ injection; approved 2017

Long acting; Wegovy only medication approved for DM and weight loss

Half life ~ 1 week

- Remember it takes 5 half-lives to eliminate a drug completely

Tachyphylaxis occurs with prolonged use with respect to effects on delayed gastric emptying (with extended use, less delayed gastric emptying; ~ 30-week mark)

Common GI side effects peak ~ 12 weeks of use and continue for up to 30 weeks of use

- Extra caution should be used during first 8-12 weeks which correlates to highest period of nausea

Medications: Mounjaro (Tirzepatide)

Tirzepatide—dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist

- Half-life is 5 days and given as once weekly SQ administration

Common GI side effects: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, constipation and decreased appetite

Side effects are generally increased with higher dosages and are common during first 4 weeks of treatment and with any dose escalation

Side effects do tend to decrease over time (same as was seen with other long acting GLP-1 RAs that are given once weekly)

Only FDA approved (2022) for the management of type 2 DM but many patients are using it “off label” for weight loss

- Per Mounjaro’s website, it states it is “not a weight loss drug”

Other GLP-1 RAs used for type 2 DM

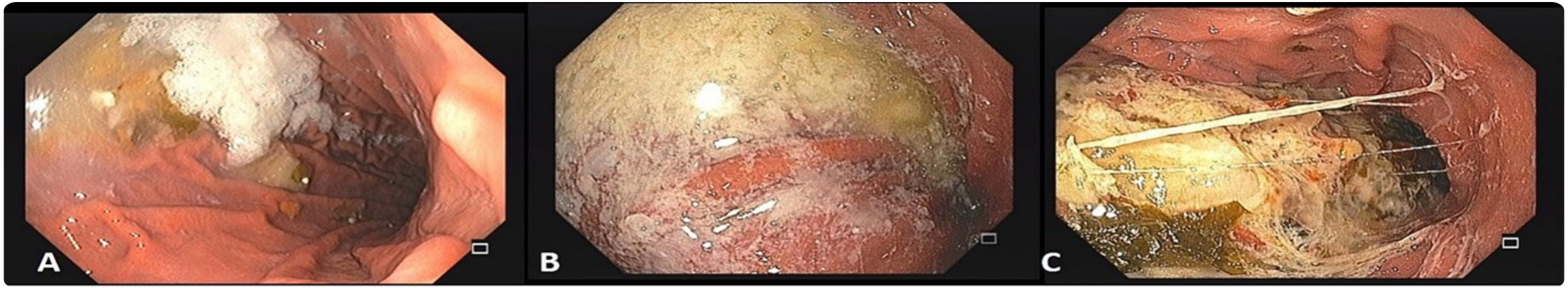
Weekly Injections	Ablbiglutide (Tanzeum) Dulaglutide (Trulicity) Exenatide ER (Bydureon)
Daily Injections	Exenatide (Byetta) Lixisenatide (Adlyxin)—Discontinued in US Jan 2023
Oral	Semaglutide (Rybelsus)—daily oral dose
Combined with insulin	Liraglutide/insulin degludec (Xultophy)—once daily Lixisenatide/ingulin glargine (Soliqua 100/33)

Current Studies

- In a study with diabetic patients and patients with cardiovagal neuropathy, GLP-1 did not influence gastric volume suggesting actions on the stomach are reliant upon vagally-induced mechanisms

Semaglutide Retrospective Study

- Study from Journal of Clinical Anesthesia by Silveira et al. (2023)
- Retrospective analysis of effects of semaglutide on residual gastric content (RGC) in patients who had taken semaglutide in past 30 days vs pts who had not undergone EGD
- Pts taking semaglutide are instructed to discontinue for 10-14 days prior to their procedure
- Fasting intervals were avg 9.3 hrs (range 5-12.8 hrs) for clear liquids and 14.5 hrs (range 12.2-28.7 hrs) for solids
- Majority of pts (87%) were taking semaglutide for weight loss
- Semaglutide use was associated with increased RGC; this association increased further in pts who were taking semaglutide and had GI sxs (n/v, dyspepsia, or abdominal distension) the day of procedure



Semaglutide Retrospective Study

- In patients who had RGC, 85% had solid content observed
- Typical rate of aspiration is 1 per every 2000-3000 anesthetics
- This case study had a sample size of 404 pts (33 in semaglutide group and 371 in non semaglutide group)
- One patient aspirated in this case study (in semaglutide group with last dose 11 days prior); DM pt who had fasted for both solids and liquids for 12.4 hrs and denied any active GI sxs pre-procedure—**remember how we discussed absence of sxs in DM pts not being potentially reliable?**
- Of the pts who had RGC the distribution was small (25.9%), moderate (25.9%), large (48.1%)
- Picture is illustration of how they quantified volume of RGC; A was considered “small”, B “moderate”, and C “large”

Semaglutide Retrospective Study

- When EGD was combined with colonoscopy, shown to have a protective effect against the increased RGC
- Theory that alterations to diet including low fiber, avoidance of seeds, clear liquid diet as well as bowel prep may help to explain the protective benefit
  - Type of food ingested also matters (why the fasting guidelines are different for full fat meals vs. not)
- May support a push for a recommendation that all patients on GLP-1 agonists should remain on a clear liquid diet the entire day before their procedure even after they have held their meds
- The authors of this case study note that the fasting intervals for all study participants were significantly longer than that currently recommended by ASA guidelines
- Debate on the validity of current ASA fasting recommendations due to exclusion of at risk pt populations and current end point of prior studies has focused on prevention of bronchial aspiration and not the assurance of an empty stomach

Study on liraglutide using capsule endocopy

- Studied patients with DM type 2 in Japan by Nakatani et al. (2017)
- Used capsule endoscopy to evaluate gastric transit times before and after liraglutide administration
- Study groups were divided into patients with known diabetic neuropathy (DN) and those without
- Diabetic neuropathy group possessed 2 out of 3 of the following to meet criteria: reduced vibratory sensation with tuning fork to lateral medial malleoli; or absent Achilles tendon reflexes; nerve pain and paresthesia in bilateral tips of toes or soles of feet
- All pts had previously not been taking liraglutide and dosages were started at 0.3 mg weekly and increased in increments of 0.3 mg weekly until the max approved dose in Japan of 0.9 mg was achieved
- Patients had their post liraglutide capsule study performed 1 week following the 0.9 mg dosage was reached (*Note how much lower the studied dosages are compared to the 3 mg dosages used for weight loss in the US and how GI side effects increase with increased dosages)
- I know I am speaking in weeks, however, this is the short acting GLP-1 that is administered daily
    - Dosage adjusted weekly, but administered SQ daily

Study on liraglutide using capsule endocopy

Gastric transit times in DN group were 1hr 12 mins pre and 48 mins post liraglutide administration which was a non significant difference (and actually **decreased** in the liraglutide group)

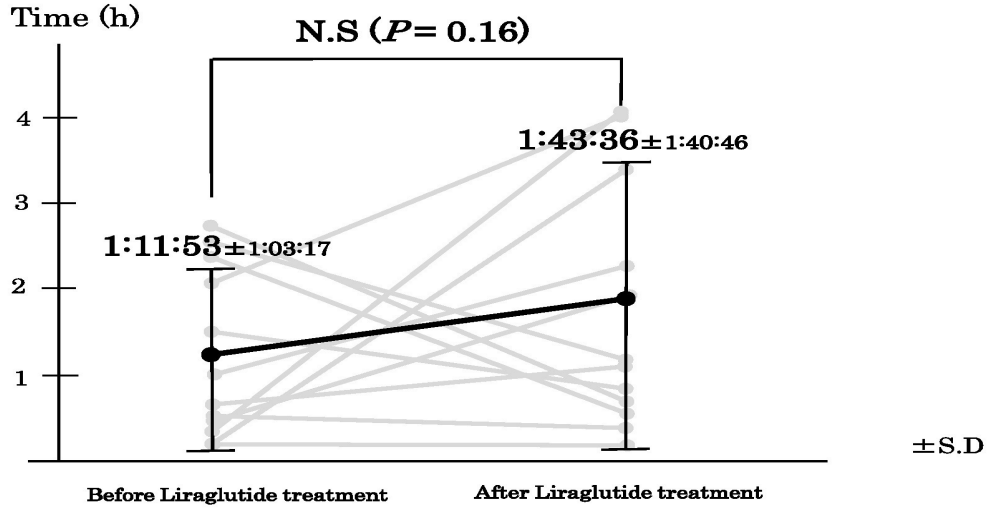
Gastric transit times in the non-DN group were 1 hr 1 min pre and 2 hrs 33 mins post liraglutide administration which was a significant increase in the gastric transit time

Small intestine transit time was 4 hrs 10 mins before and 6 hrs 38 mins post in the DN group and 3 hrs 51 mins pre and 6 hrs 45 mins post in the non-DN group

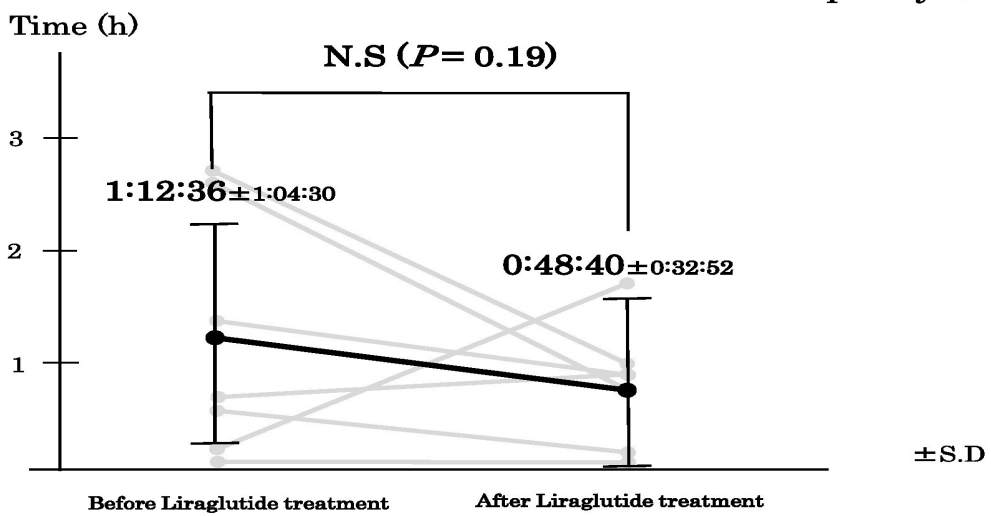
Study on liraglutide using capsule endocopy

- GI residue rate was 32% pre and 90% post liraglutide administration for the DN group
- GI residue rate was 32% pre and 78% post liraglutide in the non-DN group
- Gastric residue was evaluated using the Boston Bowel preparation scale which is used to evaluate adequacy of bowel prep during colonoscopy
- The GI residue rate was noted to increase in all patients after liraglutide administration and that finding was statistically significant
- Findings: liraglutide was shown to cause delayed gastric emptying and inhibit duodenal and small bowel motility
  - In patients with diabetic neuropathy and known dysautonomia these effects may be decreased or absent

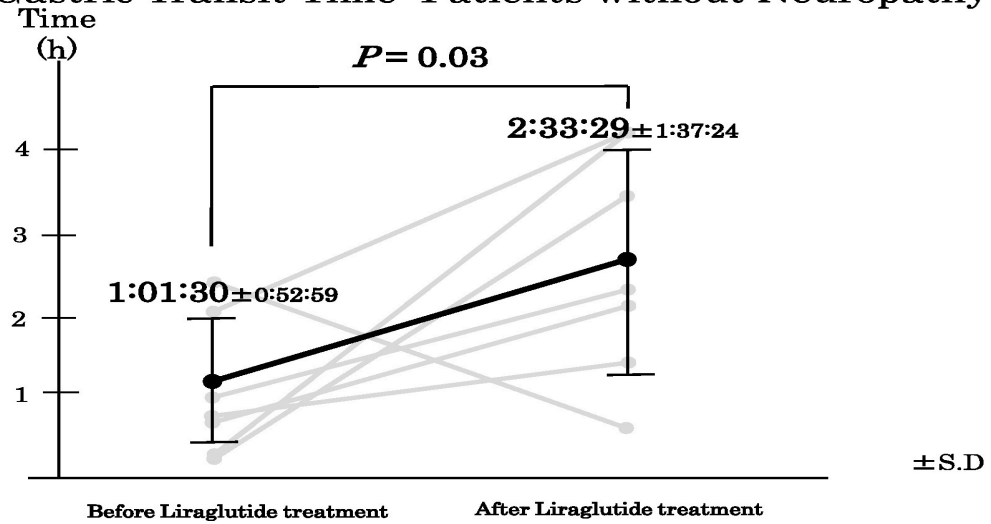
1-Gastric Transit Time: All Patients (n=14)



2- Gastric Transit Time: Patients with Neuropathy (n=7)



3- Gastric Transit Time: Patients without Neuropathy (n=7)



PoCUS Study

Study published by Sherwin et al. (2023) in the Canadian Journal of Anesthesia

Prospective study using gastric ultrasound to identify the presence of residual solids in the stomach in volunteers without obesity who recently started taking semaglutide

20 pts total, 10 in each group divided into the semaglutide and non semaglutide (control) arms

Participants fasted for 8 hrs prior to initial scan, then drank 12 oz of water and were rescanned 2 hours later

PoCUS Study

70% of semaglutide group and 10% of control group had

90% of semaglutide group and 20% of control group had

(supine position): only 30% of semaglutide participants “rated as empty” vs. 90% of control group “rated as

2 hours post water scan (lateral position): no difference in the two groups; this is interesting and somewhat concerning regarding reliability of gastric scanning in general, but impresses upon the need to scan in both supine and lateral positions

Another study concludes that this may indicate GLP-1 RAs have implications for aspiration risk during anesthesia

Gastric Residue Study

Study of diabetic patients by Kobori et al. (2023)

Study design was a matched pair case-control study

Compared diabetic patients of similar characteristics: one group was on a GLP-1 RA and the other who was not

Pts taking GLP-1 RAs had a statistically significantly higher proportion of gastric residue present on EGD

Previous studies that stated delayed gastric emptying effect with longer-acting GLP-1RAs diminished over time contradicted in this study; mean duration of use was 57 months in patients on long-acting GLP-1 RAs with gastric residue

Patients on GLP-1 RAs with increased gastric residue were statistically significantly younger in age

Anesthesia Implications

Novel uses of existing medications and medications on market for limited time pose distinct challenge for practice recommendations

There has not been a study evaluating risk benefit ratio of continuing GLP-1 RA use in perioperative period and optimal time of discontinuation

Data shows potential for significant patient harm if modifications are not made to current perioperative management of these patients

When potential adverse effects have life-threatening consequences, at some point it becomes reasonable to invoke precautionary principle…rather than assuming GLP-1 receptor agonists are safe during perioperative period, one would instead assume they may be unsafe and act accordingly (until more evidence has accrued and true problem—or lack thereof—becomes clearer (Jones et al., 2023)

ASA Recommendations

Hold GLP-1RA on day of surgery if pt is on once daily dosing

Hold GLP-1RA x 1 week if pt on weekly dosing

- Applies to patients taking it for DM and weight loss and for all surgeries/ procedures

Consideration of bridge therapy by endocrinologist for DM pts if dose is to be held longer than regularly scheduled dosing

If GI sxs are present such as severe n/v, abd pain, bloating, and retching → consider delaying if elective

If pt asymptomatic DOS but did not hold medications as recommended, proceed with full stomach precautions or consider eval with gastric US; if empty, proceed; if full or gastric US is inconclusive or not possible, consider delaying or proceed with full stomach precautions

No current evidence to dictate optimal fasting periods in these patients, so presently we should continue to follow current ASA fasting guidelines until further evidence is obtained

ASA Press Statement June 29, 2023

Conservative Approach

Consider holding GLP-1 RAs until 3 half-lives of the drugs have passed (3 weeks for longer-acting drugs like semaglutide; 39 hrs (~ 2 days) preop for shorter-acting drugs like liraglutide → **1-2 weeks at a minimum**

Consult endocrinologist for glycemic control in DM pts

Jones et al. (2023)

A "safe" fasting interval does not yet exist; increased fasting intervals are not currently recommended

- NPO times exceeding current fasting guidelines are still presenting with full stomachs

If drugs unable to be held for 3 half-lives, consider pt full stomach and perform RSI if general anesthetic is required

If pt only requires sedation, potential increased risk of regurgitation of gastric contents and consider performing RSI and GETA

Consider the use of POC gastric ultrasound to evaluate with the caution that both false positives and false negatives are possible

ASA Fasting Guidelines

*Individuals without coexisting diseases or conditions that may increase the risk for aspiration, including esophageal disorders such as significant uncontrolled reflux disease, hiatal hernia, Zenker's diverticulum, achalasia, stricture, previous gastric surgery (for example, gastric bypass), gastroparesis, diabetes mellitus, opioid use, gastrointestinal obstruction or acute intraabdominal processes, pregnancy, obesity, and emergency procedures. Exercise clinical judgment with this patient population. †Up to 400 mL of clear liquids is considered an appropriate volume. Trial participants ingested a median of 400 mL of carbohydrate-containing clear liquids (interquartile range, 300 to 400 mL) up to 2 h before anesthesia administration. ‡Chewing gum should be removed before any sedative/anesthetic is administered.

Risks

- Recent study from University of Montpellier looked at type 2 diabetes patients who were treated with GLP-1 RAs from 2006-2018
- Identified link between long-term use of these drugs and a higher likelihood of thyroid cancer
- Found that people who took the drugs for 1-3 years were 58% more likely to develop thyroid cancer
- Medullary thyroid cancer, a rare form, carried an even higher risk
  - Patients currently monitored every 3-4 months with liver, diabetes, kidney, cholesterol, and electrolyte testing
  - Thyroid testing is currently not recommended
  - No current recommendations for thyroid ultrasound or serum calcitonin monitoring

Future Medications and Issues

An oral non-peptide GLP-1 RA in development

Retatrutide: triple GLP-1, GIP, and glucagon receptor agonist is being developed for treatment of type 2 DM

****Critical drug shortages for DM patients**

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