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REVIEW

A review of anti-obesity medications and anaesthesia

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The growing use of anti-obesity medications (AOM) in an expanding population of overweight and obese patients renders these drugs of importance to the anaesthesiologist. We review the current pharmacotherapy available in South Africa, the drugs' mechanism of action (MOA), and their potential interactions and implications with various anaesthetic agents during the perioperative period.

Keywords: anti-obesity medications, anaesthesia

Introduction

Obesity is one of the fastest-growing healthcare problems of our time, with the global prevalence tripling since 1975.[1-3] In South Africa, 68% of women and 31% of men are overweight or obese.[4] These patients have a higher prevalence of cardiovascular, respiratory, endocrine (e.g. diabetes mellitus), musculoskeletal disorders and certain cancers.[5,6] AOMs, though currently under-prescribed, are increasingly utilised in this group to achieve weight loss and improve health.[7,8]

The increasing number of obese and overweight patients using AOMs and presenting for surgery means anaesthesiologists need a thorough understanding of the drugs and their effects. There has been much recent interest in the literature on the impact of glucagon-like peptide-1 (GLP-1) receptor agonists on anaesthesia, and there is older evidence regarding the impact of sympathomimetics perioperatively.[9-13] This review examines all current AOMs available in South Africa, their MOA, potential interaction with anaesthetic agents, and impact on safe anaesthesia practice.

Physiology of appetite

Weight regulation is a balance between energy expenditure and energy intake. Energy expenditure is a combination of resting basal metabolism and energy to metabolise food and perform activities.[14] Energy intake is food consumed. There is a balance between appetite and satiety, with nervous and endocrine systems integral to regulating expenditure and intake, and both central and peripheral mechanisms contribute.

The hypothalamus coordinates with the limbic, cortical, and autonomic centres centrally, and it receives peripheral inputs from the gastrointestinal tract (GIT), pancreas, liver, adipocytes, leptin, and vagus nerve.[2,5-7,16-18] The mesolimbic reward pathways interact with hypothalamic control. Increased sugar and fat intake disrupt homeostasis. Thus, emotional eating or food addiction is mitigated by neurochemistry. The chief neurotransmitter in this area is dopamine; however, opioids, gamma-aminobutyric acid (GABA), glutamate, orexin, and nicotinic cholinergic receptors have also been identified.[18] Serotonin is also a hedonistic input, and it is associated with appetite suppression and may explain why mood affects appetite.[16-19]

Peripheral inputs arise from the liver, pancreas, GIT, and adipocytes. Acute regulators are released in response to food intake, and longer-term hormones are produced in response to energy stores.[2,15,18] Communication between the central and peripheral components of the neuroendocrine system occurs via a combination of the vagus nerve, nucleus tractus solitarius, and the circulation transporting hormones.[18] Some of the peripheral inputs include (listed anatomically):

- Ghrelin, the "hunger hormone", secreted by the stomach and stimulates appetite.
- Cholecystokinin (CCK), secreted by the intestine, slows gastric emptying, stimulates gallbladder contraction, and leads to satiety.[2,15]
- Glucose-dependent insulinotropic polypeptide (GIP), released by the proximal duodenum and stimulates satiety.
- Pancreatic polypeptide, produced by the pancreas in response to intake, slows gastric emptying, and suppresses hunger.
- Fibroblast growth factor 21 (FGF21), secreted in response to fasting. It is implicated in the preference for sweet foods.[2,15]
- GLP-1, secreted in the distal bowel, acts on the hypothalamus to decrease appetite, slow gastric emptying, stimulate insulin release, and inhibit gluconeogenesis.
- Peptide YY (PYY), has similar effects to GLP-1.
- Oxyntomodulin (OXM), released by the GIT, activates GLP-1 and glucagon receptors.
- Cocaine- and amphetamine-regulated transcript (CART), released in the hypothalamus in response to nutrient absorption information and suppresses appetite.[19]

- Leptin, secreted by adipocytes, gastric mucosa, and enterocytes, and signals satiety. It also activates sympathetic outflow to increase energy expenditure.[15,16,18]
- Insulin, secreted in response to increased adipocytes, leads to reduced food intake via central mechanisms.[19]
- Amylin, secreted by the pancreas, regulates the mesolimbic dopaminergic response to food intake.[2,15,18]

In summary, energy balance is under a complex web of endocrine controls with multiple pathways coexisting.

Anti-obesity medications

Weight loss occurs when energy expenditure exceeds energy intake. AOMs reduce hunger and increase satiety, leading to a reduction in energy intake. They all work via central mechanisms, affecting the nervous system and neurochemistry, except for the lipase inhibitor, orlistat, which works exclusively in the GIT.[16]

AOMs are registered for use in obese patients with a body mass index (BMI) > 30 kg/m^2 or in overweight individuals with a BMI > 27 kg/m^2 with more than one comorbidity related to their weight, such as hypertension, diabetes, or non-alcoholic fatty liver disease.[19] Despite these United States Obesity Working Group recommendations, AOMs are utilised in only 3% of the applicable population.[18] This may be due to clinician ignorance, cost, or side effects.[18] This will likely change due to research and growing demand from an expanding patient population.[6]

A drug is an effective AOM if its use for one year results in at least a 6% reduction in total body weight (TBW). Most drugs need to be used in combination therapy to cause greater weight loss.[17-19] Many of these drugs have side effects related to their MOA, which, together with potential drug interactions, should be considered in the perioperative period. AOMs are discussed below, with a summary provided in Table I.

Peripherally acting agents

Lipase inhibitors

Orlistat (Xenical) is a pancreatic lipase inhibitor that acts on lipase released within the GIT, preventing lipid breakdown and fat uptake. Lipid is lost undigested in the stool. This drug is registered for long-term use and is affordable, but it may only be beneficial for those eating high-fat diets. As monotherapy, its effect is a modest 3% loss of TBW [2,7,18,20]

Orlistat has numerous GIT side effects: flatulence, faecal incontinence, abdominal cramps, and the decreased absorption of fat-soluble vitamins and medications. Therefore, it is contraindicated in patients who have undergone gastric bypass surgery.[2,7,18,20] Anaesthetic considerations are the reduction in vitamin K-dependent coagulation factors and, thus, increased blood loss during surgery.[20]

Centrally acting agents

Glucagon-like peptide-1 receptor agonists

Liraglutide (Saxenda, Victoza) and semaglutide (Ozempic, Wegovy) mimic hormones produced by the L-cells of the distal small intestine. They bind to receptors both centrally and in the gut, causing satiety and reducing gastric emptying.[2] By slowing stomach emptying and inhibiting postprandial acid secretion, they act as an ileal brake and further prolong gut transit times.[9] Liraglutide is the most efficacious drug of all the AOMs as monotherapy, with an average reduction of 8% in TBW. These drugs are the most expensive AOMs.[7]

Side effects commonly include fatigue, headaches, nausea, and abdominal cramps. Pancreatitis, thyroid C-cell cancers, tachycardia, and renal impairment can occur less frequently. This group is contraindicated in patients with a personal or family history of pancreatitis, thyroid malignancy, or multiple endocrine neoplasia (MEN) syndromes.[2,7]

Delayed gastric emptying from GLP-1 receptor agonists must be considered in the perioperative period.[9-11] Studies indicate solid gastric content within the stomach well beyond the current fasting guidelines of six hours. Aspiration of gastric contents during anaesthesia is a pertinent concern, but there are conflicting opinions at present.[9,21-23] Current American Society of Anesthesiologists (ASA) guidelines suggest stopping these drugs for seven days before elective surgery in agents employed weekly or for 24 hours in those administered daily.[23]

The Australian and New Zealand College of Anaesthetists (ANZCA) guidelines indicate insufficient evidence to support the cessation of GLP-1 receptor agonists before anaesthesia, as the duration of delayed gastric emptying is unknown and may be several weeks. They recommend that patients using daily injections omit these for 24 hours before anaesthesia but that all patients using these medications within four weeks preceding anaesthesia be managed per local protocols for the unfasted state. They further highlight that the absence of GIT symptoms as a side effect of GLP-1 receptor agonists does not preclude significant retention of gastric contents and aspiration risk in supposedly fasted patients.[25] They suggest a preoperative gastric ultrasound to quantify stomach contents may help the clinician to risk stratify patients. [24,25]

Preoperatively, it is also important to consider nutritional status. Patients actively losing weight are in a catabolic state and may have limited fat-soluble vitamins, iron, and protein, which may all impair wound healing and predispose them to sepsis.[20]

Opioid receptor antagonists and dopamine-noradrenaline reuptake inhibitors

Naltrexone/bupropion (Contrave) is a combination drug that contains an opioid receptor antagonist, naltrexone, and a dopamine-noradrenaline reuptake inhibitor (DNRI), bupropion. Naltrexone is commonly used to manage long-term opiate addiction. It is also thought to inhibit the reward centres involved

Table I: Current anti-obesity medications

Drug	Trade names	Mechanism of action	Contraindications	Side effects	Drug interactions	Cost ±	Dose	Formulation
Orlistat	Xenical	Lipase inhibitor	Short gut syndrome, post gastric bypass	Gastrointestinal tract side effects Vitamin A, D, E, and K deficiency	Anti-coagulants	R17.31 to R51.93 per day	Up to 120 mg three times daily	Oral
Naltrexone Buproprion	Contrave	Opioid antagonist and dopamine/noradrenaline reuptake inhibitor	Hypertension Seizures Drug or alcohol abuse	Hypertension Seizures Hepatoxicity Nausea and vomiting	Opioids Monoamine oxidase inhibitors	R11.90 per day	8 mg/90 mg daily	Oral
Liraglutide Semaglutide	Saxenda Victoza Ozempic	Glucagon-like peptide-1 agonists	Multiple endocrine neoplasia Thyroid malignancy Pancreatitis	Headache Nausea Vomiting Diarrhoea	Warfarin may affect absorption of other oral medications	R995.49 to R6 000 per week Some not available in South Africa	0.6–3 mg weekly 0.5–2 mg weekly 3–14 mg daily	Subcutaneous injection Oral
Phentermine	Duromine	Sympathomimetic amine	Ischaemic heart disease Hypertension	Hypertension Anxiety Dizziness Insomnia	Alcohol Monoamine oxidase inhibitors	R18.24 to R36.48 per day	15–30 mg daily	Oral
Lisdexamfetamine	Vyvanse	Amphetamine prodrug	Phaeochromocytoma Cardiovascular disease	Hypertension Tachycardia Insomnia Irritability Anxiety	Monoamine oxidase inhibitors Selective serotonin reuptake inhibitors	R36.47 per day	70 mg daily	Oral
Metformin	Glucophage	Biguanide	Renal impairment	Hypoglycaemia Nausea Vomiting	Alcohol Corticosteroids	R0.82 to R3.50 per day	500–2 000 mg daily	Oral
Dapagliflozin Empagliflozin	Forxiga Jardiance	Sodium-glucose linked_ transporter Alpha-inhibitors	Renal impairment	Hypovolaemia Urinary tract infections Hyperkalaemia Diabetic ketoacidosis	Rifampicin Ketoconazole	R50 to R100 per day	10 mg daily	Oral

in appetite and feeding. It has been employed in weight loss therapy in low doses and is particularly useful in combination with DNRIs as they seem to act synergistically. DNRIs, often used in depression, attention-deficit/hyperactivity disorder (ADHD), and Parkinson's disease, block dopamine and noradrenaline transporters in the synaptic cleft leading to increased concentrations of both with greater effect.[2,7]

Contrave use can achieve an average TBW loss of 3%. It is a cheaper option, at a quarter of the cost of the GLP-1 inhibitors, and approved for long-term use. It is the agent of choice in those patients with depression or who are quitting smoking.[2,7,15] Contrave's side effects are due to increased dopamine and noradrenaline and include elevated blood pressure, tachycardia, raised intraocular pressure, an increased propensity for seizures, dry mouth, headaches, nausea, and vomiting. Subsequently, this class of AOM is contraindicated in patients with hypertension, seizure disorders, glaucoma, alcohol misuse, or chronic opioid use.[2,7] There are also risks for drug interactions with other medications that lower the seizure threshold (neuroleptics, steroids, antidepressants, theophylline) and a risk of severe hypertensive reactions in patients taking monoamine oxidase inhibitors.

The most troublesome anaesthetic implication of this drug class is opioid tolerance due to naltrexone-induced opioid receptor antagonism. Patients on this medication may require higher doses of opioids, and it is advised that these patients be offered multimodal analgesia and opioid-sparing analgesic techniques. It is advised that patients stop naltrexone medications two hours before surgery.[26] In all cases, the risk of sedation and respiratory depression due to the up-regulation of central opioid receptors exists, and these patients should be

monitored in a high-care unit while on opioid therapy until safe dosing has been established.[27]

While naltrexone can be discontinued abruptly, the rapid discontinuation of bupropion may lead to withdrawal symptoms, hypertension, and delirium. Postoperatively, if treatment is restarted, the dose must be tapered upwards over four weeks.

Sympathomimetic amines

Phentermine (MINEX, Duromine) has some pharmacodynamic similarity to its parent compound, amphetamine, releasing noradrenaline and, to a lesser extent, dopamine and serotonin at the synaptic cleft. This causes central stimulation of satiety and peripherally stimulating lipolysis and thermogenesis. It is the oldest AOM and affordable, but it contributes to only a 4% loss of TBW when used in isolation. It is only registered for short-term use for a maximum of 12 weeks, and tolerance may occur.[2,7,12]

Phentermine commonly causes cardiovascular side effects like palpitations, hypertension, and tachycardia, and it carries a small risk of angina and myocardial infarction. It may also cause anxiety, headaches, insomnia, and, rarely, psychosis. It frequently causes nausea, vomiting, abdominal pain, and a dry mouth. It is contraindicated in patients using recreational drugs, monoamine oxidase inhibitors, or in patients with hypertension, hyperthyroidism, or ischaemic heart disease.[12]

The primary anaesthetic concern is perioperative hypotension. The ASA advises this drug to be omitted for a minimum of four days before elective surgery.[12] In patients who have taken this drug up to the time of surgery, direct-acting vasopressors or inotropes should be used as first-line management of hypotension. Phentermine also carries the risk of serotonin syndrome when used with drugs such as tramadol or pethidine, and it may inhibit the effects of alpha-2 agonists.[12]

Sympathomimetic amine and GABA receptor modulators

Phentermine/topiramate (Qsymia) is a combination drug that incorporates the synergistic effects of phentermine and a GABA receptor modulator topiramate. Topiramate is an excellent antiepileptic and migraine therapy. Its MOA in weight loss is poorly understood. It is modestly effective in isolation, but it averages a 7% loss in TBW in combination with phentermine. Qsymia is registered for long-term use.[2,7,12,15]

Side effects are those of phentermine plus hypokalaemia, peripheral neuropathies in vulnerable patients, and seizures and delirium with rapid discontinuation. The anaesthetic implications are the same as those of phentermine.[2,7,15]

Amphetamine products

Lisdexamfetamine (Vyvanse) is a prodrug converted in the bloodstream by lysine to dextroamphetamine. It is used to treat ADHD in children but is also used for binge eating in adults. It acts centrally to stimulate satiety, like sympathomimetic amines, but has a sustained release and less potential for abuse as a stimulant.[2,7,15]

Side effects include insomnia, irritation, anxiety, hypertension, and tachycardia. It is contraindicated in cardiovascular disease. Perioperative use can lead to hypertension and tachycardia. It is costly, and there are worldwide shortages.

Biguanides

Metformin (Glucophage) reduces gluconeogenesis in the liver, thus reducing plasma glucose. It also increases insulin sensitivity and glucose uptake by the tissues. The proposed mechanism of weight loss is via hypothalamic modulation of appetite regulation centres, but this is currently not completely understood. It is by far the cheapest AOM on the market and the most frequently employed.

Side effects of diarrhoea, nausea, and vomiting occur commonly. Metformin is contraindicated in patients with chronic kidney disease. There is a theoretical low risk of perioperative lactic acidosis.[5-8,15,18]

Sodium-glucose transport protein 2 inhibitors

The gliflozins (dapagliflozin [Forxiga], empagliflozin [Jardiance], and canagliflozin [Invokana]) act on the nephron's semisynthetic glucagon-like peptide-2 (SGLP-2) receptors, inhibiting glucose reuptake, thereby lowering blood sugar. They are used in diabetics with concomitant cardiovascular disease. They may lead to modest weight loss but are better at treating hyperglycaemia. They are affordable and have the benefit of reducing the risk of major adverse cardiovascular events in at-risk patients. They are contraindicated in patients with chronic kidney disease.

Side effects include hyperkalaemia, hypovolaemia, and euglycemic diabetic ketoacidosis. To limit these potential side effects, the ASA recommends cessation of these agents three days before elective surgery.[5-8,15]

Amylin analogues

Pramlintide (Symlin) mimics endogenous secreted pancreatic hormones, stimulates satiety centres, and slows gastric emptying. Its major risk is aspiration under anaesthesia. This drug is a novel agent, and much research is ongoing on its efficiency and tolerability.[15,18]

Cannabinoid receptor-1 antagonists

Rimonabant (Serenade) has shown promise in weight loss in rodent studies. It targets central reward pathways involved in feeding. Human studies indicated a clinically significant increased risk of depression and suicidal ideation anxiety, and it was withdrawn from the market.[15,18]

Proopiomelanocortin activators

Lorcaserin (Belviq) is a selective serotonin 5-hydroxytryptamine receptor 2C (5-HT2C) receptor that acts centrally to induce satiety. Studies indicate an average weight loss of 3% from baseline. It held promise in obesity management in patients

with depression, but early trials showed an increased incidence of cancer, and the drug was withdrawn.[15,18]

Conclusion

AOMs are a diverse group of drugs that show immense promise in assisting with weight loss and management in overweight and obese patients. They have further independent benefits of limiting insulin resistance, lipid levels, and blood pressure. Though currently under-prescribed, growing knowledge of and access to these drugs means that the anaesthesiologist must be aware of the implications of their use in the perioperative setting and be able to advise the patient using them regarding appropriate cessation or particular risk.

Conflict of interest

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