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DRUGS AFFECTING THE GASTROINTESTINAL SYSTEM

SUNALI MEHTA

Histamines and antihistamines:

Histamine means tissue amine and is present in ample amount in the lung, skin and GI tract mucosa. Mast cells, basophils and platelets contain histamine in an inactive bound form. It is derived from the aa histadine by decarboxylation. Two functions are : control of microcirculation and secretion of HCl from the parietal cells of the stomach. It causes vasodilation. This can help in an immune response where the inc in capillary permeability can help in the movement of immunocompetent cells and other immunological mediators to the site of injury.

Local release of histamine in the nasal pathway due to the stimulation by a pollen grain can lead to hayfever.

Release of histamine in the skin due to an insect bite can lead to urticaria.

Destruction of many cells by some cause can also lead to a release in the amount of histamine.

Histamine reacts with receptors to cause a response. Two types of receptors have been identified and are h1 and h2. the h1 receptor is found in the smooth muscle of the bronchioles and exocrine glands of the respiratory tract. The h2 receptor is found in the parietal cells of the stomach. Both the receptors are found in the CNS and heart, where the h2 receptor has a positive chronotropic effect whereas the h1 has both positive chronotropic and inotropic.

Chronotropic: something that alters the rate of heart beat

Inotropic: something that alters the force of contraction of the heart.

The term antihistamines are used for H1 blockers or antagonists. And for the h2 receptor there is the h2 blocker or antagonist. They not only block the histamine receptor but also inhibit the release of histamine from the mast cells. Initially all histamines were able to cross the bbb hence had the sedative effect. The main side effect being dry mouth and sedation. These are mainly used to treat allergies and anaphylaxis reactions.

Antiemetics: to treat Nausea and Vomiting:

Whatever be the cause of nausea and vomiting the vomiting center in the brain is involved. The treatment of this condition depends on the cause. Many of the cases of nausea and vomiting is a protective function of the Chemoreceptor Trigger Zone (CTZ) responding to a therapeutic drug. The ctz situated near the vomiting center in the medulla is protected by the bbb. Due to both a mechanical or a chemical stimulation of the GI tract vomiting can occur and both of these are protective mechanism.

Drugs used to treat Nausea and vomiting:

To treat vomiting suppositories are convenient whereas in the case of nausea the cause is determined and is prevented then being cured. When nausea and vomiting is due to the psychogenic factors involving the cortical center of the brain the use of benzodiazepine is useful as a sedative.

Antimuscarinic drugs:

The only antimuscarinic drug used to treat against emetics is **hyoscine** and is used in the treatment of motion sickness. It is available in various forms and is an effective way of treatment. It has a long lasting effect.

Antihistamines:

Any antihistamine will have an antiemetic property although only a few are used. They are better than antimuscarinic agents. They can be used for travel sickness and at the same time for other type of nausea such as Menieres disease and labyrinthitis. It can cause drowsiness which can be troublesome.

Phenothiazines:

In practice the only phenothiazine that is used is prochlorperazine and is mainly used to treat against motion sickness. It can cause extrapyramidal symptoms and oculogyric crises as an adverse reaction. The drug induces photosensitivity if taken more than 4 times in 24 hours.

Metoclopramide and domperidone:

They reduce the stimulation of the CTZ and as a result prevent nausea and vomiting, they also inc the rate of gastric emptying and dec the sensitivity of the receptors in the pharynx and upper gut to noxious stimuli.

The setrons: ondansetron: are serotonin antagonists that are highly effective for 5 – HT3 receptors found on the afferent fibers of the vagus nerve and in the brain associated with the ctz. These receptors when blocked help to control chemically induced vomiting and nausea. These are used in controlling the vomiting associated with cytotoxic drugs. These are relatively free of side effects except for a mild transient headache and sometimes may cause diarrhea or constipation.

Nausea and vomiting In pregnancy is common in the first trimester and can be extended too. It is best treated with ginger and or pyridoxine but this has an implication of being teratogenic. The best used drug is an antihistamine doxylamine.

Drugs used to induce vomiting include emetine which is the active ingredient of ipecacuanha. It induces vomiting by irritating the upper gut and on absorption acts on the ctz.

Nausea and vomiting can occur whenever the stomach is overly irritated, stimulated or distended and are common non – specific features of disease or drug toxicity.

Drugs to know:

Metoclopramide - Dopamine antagonist

Chlorpromazine – phenothiazine

Prochlorperazine – phenothiazine

Promethazine - Antihistamine

Atropine - antimuscarinic

Odansetron – steron

There are specific receptors present in the two centers in the brain, in the vomiting center there are the muscarinic receptors and H1 receptors that are present and these are triggered when Ach and histamine bind to them respectively. In the CTZ there are the dopamine receptors and the 5HT3 receptors and these will be stimulated when dopamine and serotonin bind to them respectively leading to the trigger of the vomiting center leading to the emesis. The 5 HT3 receptors are also present in the pharynx, biliary tree and intestine.

Antiulcer drugs and antacids: upper GI tract drugs:

The most common problem associated with the stomach is the secretion of excess acid. the stomach is well protected with the mucosal cells from the acid

and proteinase pepsin. When there is a damage of the mucosal layer erosion can occur in the gastric mucosa leading to a gastric ulcer. When this acid enters the duodenum it can cause duodenal ulcer. In some cases there can be further erosion and the fluid can leak into the peritoneal cavity leading to life threatening peritonitis. When the acid enter the oesophagus a burning sensation is felt and this is commonly termed as a heart burn and is treated with an antacid.

Antacids:

Mechanism of action: are weak bases which readily combine with the HCl and neutralize it. They also raise the pH of the stomach and over a pH of 4 pepsin is inactive. There are usually basic compounds of Al, Na, Ca, Mg and K. normally used are AlOH and MgCO₂ in combination. These are mixed in a correct proportion to nullify the effect of al causing constipation and mg acting as a laxative. E.g. hydrotalcite.

AlOH complexes with phosphate in the gut and is useful in the treatment of hyperphosphatemia that can result from renal failure. It can lead to hypophosphatemia.

Mgtrisilicate is found in some antacids and when neutralized with HCl produces a viscous jelly which is said to coat and protect the peptic ulcer promoting healing. When used alone it is not very protective.

Calcium carbonate: is used in several antacids and overuse can lead to high level of ca in the blood but cant cause hypercalcaemia, these can over a long period of time lead to calcification of the soft tissue and the development of kidney stones.

Sodium bicarbonate: baking soda: the release of carbon dioxide from the neutrilisation of sodium bicarbonate can lead to burping which many think to be a cure. The use should not be encouraged as sodium can exacerbate the pre – existing conditions of hypertension and also can lead to alkalosis by excessive absorption of bicarbonate ions.

Alginates: Gaviscon, Mylanta plus, meracote, aligcon: these are derived from a seaweed and when they react with the acid they form a jelly like substance that floats on the aqueous solution. This property gives these antacids the name raft antacids. It floats upto the top and prevent s a gastric reflux but in some positions it might float upto the cardia of the stomach and prevention of a gastric reflux will be tough.

Oxethazaine: is a local anaesthetic that is included in the preparation of the antacid Mucaine and is useful when the antacid alone do not relieve the pain of indigestion.

Cisapride: it is useful in the treatment of the UGI tract conditions caused by motility problem such as reflux oesophagitis and gastroparesis. It is termed as a prokinetic drug as it accelerates the movement of the material through the stomach and the upper GI tract. It is highly selective cholinergic agent and works on the myenteric plexus and inc the release of Ach and this in turn stimulates the movement of the gut.

Peptic Ulcer:

There are three receptors in the stomach that needs to be stimulated for the production of acid they are H₂ histamine receptor, muscarinic cholinergic receptors and gastrin receptors. Gastric ulcers are mainly due to a defect in mucus production whereas duodenal ulcers are due to excessive acid production. The use of colloidal bismuth in combination of two antibacterials for the treatment of gastric ulcer due to the cause of a bacteria is known as triple therapy.

Histamine H₂ receptor antagonist:

Acid secretion is by the stimulation of the h2 receptor and hence an antagonist to this will prove to be helpful. E.g. Cimetidine there is a high relapse rate after discontinuation of the drug. Most common side effects are muscular pain, headache, dizziness.

It can slow down the metabolism of other drugs, resulting in an enhanced action. Other three H2 antagonists are ranitidine, nizatidine and famotidine. Similar to cimetidine but have no antiandrogenic activity.

Proton Pump Inhibitors:

The formation of HCl depends on a supply of hydrogen ions being produced in the parietal cells and these drugs stop this from happening. Omeprazole being the prototype. As a non-competitive inhibitor of the gastric ATPase enzyme they have a relatively long duration of action in spite of their short half-lives. They need an acidic environment to be active hence act only in the stomach.

These drugs lead to hypochlorhydria which leads to an inc gastrin secretion. Can be considered as destroying the body defence mechanism against infection.

Prostaglandins:

Action of pg on the digestive functions are:

Inhibition of gastric acid pdtn, gastrin pdtn, pepsinogen pdtn, stimulation of mucus secretion, bicarbonate secretion and inc in mucosal blood flow.

The pg analogue misoprostol is the one usually considered and has been useful where the h2 antagonists have not been very useful. It can cause diarrhea, and can have some effects on the uterus where it can cause menorrhagia.

It is contraindicated in pregnancy as it can induce premature labor by increasing uterine contraction.

Sucralfate:

Is a complex of the sugar sucrose and an Al compound. Acts only in the presence of acid. It polymerises to form a thick – paste like substance which adheres to the gastric mucosa and protects it from the acid. its adverse reaction is constipation as it is poorly absorbed.

Drugs to know:

H2 receptor antagonist – cimetidine, nizatidine, ranitidine

Proton – pump inhibitor – omeprazole

Antacids – aloh, mgoh

Bismuth compounds

Sucralfate

Misoprostol – pg

Antibiotics necessary for the treatment against H. Pyroli

Anti – diarrhea drugs and laxatives:

Laxatives: also called as aperients or purgatives. Prolonged bowel movement as in weekly cannot be termed as constipation if there is no pain associated with it and hence there is no need of a laxative, but when there is much pain associated with the bowel movement then it is termed as constipation and may require the use of laxatives.

Many drugs like antimuscarinic agents can slow down the bowel movements and lead to constipation. Narcotic analgesics can stimulate the mixing movement and as result of which there can be more water reabsorption leading to constipation. Prolonged constipation can lead to impacted faeces.

Osmotic Laxative: act by physical mechanism. Small molecules are inefficiently absorbed by the small intestine thus creating a stronger solution in the colon where lot of water reabsorption takes place. The contents are hypertonic causing the water to be retained and if the osmotic pressure is great can pull the water from the bowel capillaries back into the bowel lumen , as a result there is a rise in

the pressure and volume in the colon and rectum leading to stimulation of defecation. E.g. salts of magnesium and sodium, Epsom salts. These laxatives are contraindicated in persons with renal pathologies since there can be absorption and accumulation of the ions in the blood.

Carbohydrate osmotic laxatives:

Some sugar derivatives are not absorbed from the gut and hence can have an laxative effect. Lactulose a derivative of lactose is one of them. Some of this is metabolized by the bacterial flora of the gut into various acidic compounds which can also have a stimulant effect on the bowel walls. Glycerol when given as a suppository can also have an osmotic effect. Sorbitol also.

Flatulence and abdominal discomfort can occur with lactulose. And sorbitol can lead to diarrhea if consumed in excess.

Miscellaneous agents: used to completely empty the bowel prior to surgery.

These contain large amounts of polyethylene glycols and non – electrolytes in combination with equivalent amount of normal electrolyte such as K, Na and Cl ions. This solution is isotonic and promotes no nett loss of electrolyte or of water but effectively cleans the bowel.

Stimulant laxatives: these have a direct effect on the walls of the small and large intestine and cause an increase in the peristaltic effect leading to defecation.

Theories postulated include:

Interference with an enzyme system involved in ion transport

Inc the concentration of intestinal fluid leading to an osmotic effect.

Prevent water reabsorption into the colon and may promote water excretion directly from the intestinal cells into the lumen.

Irritate the smooth muscle of the intestinal walls leading to defecation

Adverse reaction is rebound constipation and this is since the intestine are strongly stimulated and then when the normal food stimulates it is not enough for the brain to cause enough bowel movements.

e.g. Bisacodyl – related to phenolphthalein

Castor oil - not used much today – to be metabolized to ricinoleic acid that can stimulate the smooth muscle and act as a intestinal irritant.

Sennosides – group of plant pdts.

Faecal Softeners:

Also known as emollients, surfactants or stool softeners.

Sodium dioctyl sulphosuccinate – docusate. This compound has detergent – like properties and seems to act to hold the water molecules in the faecal material thus rendering them softer and easy to pass.

Poloxalkol – is an non – ionic complex organic polymer and having similar properties to the former.

These might have some stimulant properties. And they can enhance the activity of the drugs administered concurrently with them. They take several days for their action to be noticed. Can be hepatotoxic.

Lubricants: include mineral oil namely liquid paraffin. Physical action and the oils are relatively inert. Its mode of action is that it coats the intestinal mucosa and there by prevents the absorption of water, and hence its stool softening effect. It can interfere with the absorption of fat soluble vitamins.

Anti – diarrhea drugs:

Diarrhea is defined as an inc in volume, fluidity or frequency of bowel movements relative to the usual pattern for a particular individual. First line of treatment is rehydration and electrolyte replacement therapy.

Antibiotics are not used unless the cause is well identified. Travelers diarrhea is caused by a unknown strain of E. Coli and in some cases doxycycline or

ciprofloxacin are recommended. The drugs used in the treatment of non-specific diarrhea usually slow down GI motility or help absorb the excessive fluid present in the colon.

Non-specific anti-diarrhoeal drugs:

Opioids: most of the narcotic analgesics can act on the opioid receptors in the gut and inc the mixing movement of the gut and simultaneously dec the peristaltic movement. This results in the slow down of the forward movement, improved reabsorption and as a result inc viscosity correcting the diarrhea. Very low doses are needed hence chances of addiction are low. Codeine as a syrup is used.

Morphine is also used. Lomotil is mixed with atropine to counterindicate the euphoric effect of the narcotic. Loperamide is a synthetic narcotic which is used but since it does not cross the bbb it has a very low potential to be abused. Adverse effect : constipation associated with nausea, vomiting and abdominal cramping.

Adsorbents: bismuth salts, kaolin and pectin have the ability to absorb bacterial toxin that might be implicated in causing diarrhea.

Drugs to know:

Loperamide – Immodium

Atropine

Kaolin

Methylcellulose brand

Lactulose

Senna

Docusate sodium

Phenolphthalein