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Review Article
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An Overview on Zollinger Ellison Syndrome

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Zollinger Elliosn Syndrome a rare disorder caused by excessive secretion of hormone gastrin,leading to ulceration and sometimes tumours in duodenum,this article focuses on different modes of treatment available to treat Zollinger Ellison syndrome in the system of medication in allopathy, Ayurveda , homeopathy ,etc

Key words: Pantoprazole, Treatment, Ayurveda.

INTRODUCTION

Zollinger-Ellison syndrome is a rare disorder caused by a tumor called a gastrinoma. The tumor secretes the hormone gastrin, which causes excess production of gastric acid, leading to severe recurrent ulcers of the esophagus,stomach, duodenum, and jejunum. The rarity of the syndrome,may render the diagnosis difficult to make, especially since most radiologists are not aware of this entity[1]. Since the seminal description of this syndrome in 1955 , reports worldwide have better defined the manifestations of disease, approach to tumour staging, surgical management and, in a few studies, long-term outcome has been prospectively assessed . Studies characterizing these patients from the United States have been primarily limited to extensive work from the National Institutes of Health (NIH) . The purpose of our study, therefore, was to characterise the clinical presentation, response to therapy and long-term outcome of our prospectively collected ZES cohort[2].

Problem, Zollinger Ellison Syndrome, ZES (or gastrinoma) is a rare neuroendocrine tumor of the pancreas or duodenum with an estimated annual incidence of about 0.5 per million.2 The disease was first described in 1955 by Zollinger and Ellison as consisting of the following triad: (1) gastric acid hypersecretion in the presence of (2) fasting serum hypergastrinemia with (3) resultant fulminant peptic ulcer disease and diarrhea. Although many patients with ZES present with more severe or complicated symptoms of peptic ulcer disease than patients with idiopathic ulceration (eg, approximately 7% present with perforation), the vast majority of ZES patients are indistinguishable from idiopathic acid-peptic patients. Consequently, with the ubiquitous availability of PPI therapy, many patients with ZES are likely to be treated empirically early on in the disease course, leading to improvement in their symptoms and a potential lost opportunity for diagnosis before the development of metastatic disease. In fact, older studies have shown that the mean time to diagnosis after symptoms develop is well over 6 years, and a recent combined study from the National Institutes of Health and Italian investigators revealed a declining rate of diagnosis and referral for ZES, possibly as a consequence of masking resulting from early empiric therapy with acid suppression. As mentioned earlier, the primary danger of delaying the diagnosis of ZES is that, despite control of the hormonal syndrome (which actually may be suboptimal without gastric analysis on therapy), these patients still have a significant risk of tumor progression with the development of metastases and consequently a negative outcome over time. It has been well established that early diagnosis and surgical intervention for possible cure in appropriately selected patient has a positive outcome with a roughly 30% to 40% cure rate, and an improved long-term outcome whether biochemical cure is achieved or not. In addition, most authorities believe that tumor debulking early on in the disease process also may lead to an improved long-term outcome. Patients who undergo surgical resection with a resultant biochemical cure have a 90% chance of remaining disease-free after 3 years of follow-up evaluation. Patients with ZES and multiple endocrine neoplasia syndrome type 1

(MEN-1), which occurs in about one quarter to one third of patients with ZES, may not necessarily benefit from early surgical intervention because cure is unlikely, although surgical intervention generally is performed if there is a pancreatic mass of 2.5 cm or more in size. It also should be noted that certain authorities favor nonsurgical management for the majority of individuals, citing a generally good prognosis for the vast majority of patients without surgical intervention, staging limitations at many institutions that may lack certain imaging modalities, and the failure of surgery to impact on the outcome in most patients unless they receive treatment at a center of excellence by an experienced surgeon or have a symptomatic mass lesion [3].
The non-beta-islet-cell tumour which is usually found in the Zollinger-Ellison syndrome produces a powerful gastric secretagogue which is thought to be gastrin (Gregory et al. 1967, Mc Guigan and Trudeau 1968). The tumour is malignant in about 60% of cases (Ellison and Wilson 1964), and metastases are usually to local lymphnodes and the liver. [4]

REVIEW OF SOME LITERATURES RELATED TO ZOLLINGER ELLISON SYNDROME:

a) Shou-jiang Tang,et al.,.Reported that, Zollinger–Ellison (ZE)syndrome is characterized by gastricacid hypersecretion and ulcer disease from autologous gastrin secretionbyagastrinoma. A 43year old man underwent tupper endoscopy for a 6 week history of recurrent nausea, vomiting, heartburn, weightloss, and watery diarrhea. Endoscopic findings included severere flux esophagitis with multiple line aresopha- geal ulcerations, thickened gastricfolds with mosaicpatternmucosa, distinctive gastriccorpus and antrum junction,numerous antral erosions with traces of coffee ground substance,bulbar erosions and ulcerations, and post-bulbar erosion sandul cerations. Based on these symptoms and endoscopic findings, agastrinoma work-up was institute and the diagnosis was confirmed. Endoscopists need to be aware of the classical symptoms and clinical findings associated with ZE syndrome in order to appropriately diagnose and manage affected patients. [5]

b) C Mel Wilcox et al,Reported that, Recent series describing the clinical presentation, response to therapy, and long-term outcome of Zollinger–Ellison syndrome are limited. To assess the clinical characteristics and long-term outcome of patients with Zollinger–Ellison
syndrome. Over a 20-year period, patients with Zollinger–Ellison syndrome were enrolled in a prospective trial evaluating the efficacy of lansoprazole. Following dose stabilization, patients were followed on a 6- monthly basis with interval history, physical examination, endoscopy with gastric biopsies, gastric acid analysis and laboratory studies. 72 patients (mean age 54±12 years, % male 58%, % Caucasian 69%) were prospectively enrolled.
The clinical presentation was stereotypical for Zollinger–Ellison syndrome. Symptoms had been reported for a median of 9 years prior to diagnosis. Cross-sectional abdominal imaging was often negative for demonstrable tumour. All patients had gastric acid hypersecretion controlled with variable doses of lansoprazole (median dose 60 mg/day, range 15–480 mg/day). The median survival from the time of diagnosis was 6.6 years; only two of 19 deaths were due to metastatic gastrinoma. The clinical presentation of Zollinger–Ellison syndrome was similar to prior reports. Acid hypersecretion was controlled in all patients with variable doses of lansoprazole. Long-term survival was principally related to underlying co-morbidity [6].

c) Jens F. Rehfeld,et al,Reported that, Zollinger–Ellison syndrome (ZES) is characterized by hypersecretion of gastric acid, severe peptic ulcerations in the upper small intestine, and diarrhea. It is usually diagnosed by measuring increased levels of gastrin in plasma. We examined the accuracy of commercial kits to measure gastrin (7radioimmunoassays and 5 enzyme-linked immunosorbent assays), using plasma from 40 patients suspected or known to have ZES. Each sample was analyzed using the 12 kits and a reference assay that measures bioactive gastrin in plasma, irrespective of size and

amino acid derivatization. Known concentrations of peptides with identical sequences to circulating gastrins were also assessed by all assays. Molecular patterns in plasma from patients with ZES were examined by chromatography and monitored by kits that measure false-low or falsehigh concentrations of gastrin. Failure to diagnose gastrinomas has serious consequences. Four kits found false-low concentrations of gastrin in 20% to 80% of the patients. Specificity assessment showed that the antibodies used in these kits bound only gastrin-17. Three kits found false-high concentrations of gastrin,because the reagents had increased reactions to sulfated gastrins or to unspecific factors in plasma. Thus, only 5 of 12 kits tested accurately measure plasma concentrations of gastrin. Seven of 12 tested commercial kits inaccurately measure plasma concentrations of gastrin; these assays used antibodies with inappropriate specificity that were insufficiently validated. Misdiagnosis of gastrinoma based on lack of specificity of assays for gastrin results in ineffective or inappropriate therapy for patients with ZES [7]

d) Rong-Hsin Yang, MD,et al Reported that.,. Zollinger-Ellison syndrome is a complex condition in which one or more tumors form in the patient's pancreas or upper duodenum. These tumors, called gastrinomas, secrete excessive amounts of gastrin, and almost all develop ulcers. The vast majority of gastrinomas are present within the "gastrinoma triangle,"
which is composed of the porta hepatis, duodenal sweep, and pancreatic head. As surgery remains the treatment of choice, localization of the primary lesion is often challenging but essential. We present a 50-year-old man with a tentative diagnosis of Zollinger-Ellison syndrome. His In-111 pentetreotide scan, fused onto a Tc-99m abdomen image, revealed an avid lesion adjacent to the duodenal loop. Operative resection was performed, and a primary pancreatic gastrinoma was diagnosed by immunohistochemical staining. The neuroendocrine tumors have somatostatin receptors upon them. Therefore, a penteteotide scan, using In-111 radiolabelled somatostatin analogues, is the current technique of choice. This dual-isotope display permits a visual perception of anatomic landmarks around the lesion.[8]

e) E. Christopher Ellison, et al Reported that .,. Medical treatment of the Zollinger-Ellison syndrome has been generally accepted because of the proven efficacy of the histamine (Hz)' receptor antagonists in achieving symptomatic relief, and because of early reports indicating that few, if any, gastrinomas were resectable for cure. Gastrin radioimmunoassay (WA) has made earlier and more certain diagnosis possible, and therefore reevaluation of the surgical management of gastrinomas is necessary. Experience with 60 gastrinoma patients is reported. Comparison between the pregastrin RIA years (before 1970) and post-gastrin RIA years was made to determine whether there was evidence to support the continuation of medical treatment without attempts to resect the gastrinoma. Twenty-five cases were diagnosed in the pre-RIA years. Age at diagnosis ranged from 17 to 66 years (median, 45 years). All patients were operated on. Metastases were found in 56 percent. No tumor was identified in 6 percent. Tumor was resected for "cure" (normal fasting gastrin levels for two years postoperatively) in one patient. Seventeen patients have died, and tumor was the cause of death in 70 percent. The five-year survival rate was 44 percent; the W-year survival rate was 40 percent. Thirty-five cases were diagnosed after 1970. Age at diagnosis ranged from 39 to 61 years (median,46 years). Thirty patients were operated on. Metastases were identified in 23 percent and no tumor was found in 17 percent. Tumor was resected for "cure" in 30 percent of patients. Seven patients have died and tumor caused death in 42 percent. The five-year survival rate was 62 percent; the Ml-year rate was 64 percent. Advances in diagnosis and surgical technique since 1970 have made early operative treatment applicable in patients with gastrinoma. Because death in most cases is caused by progression of the tumor, an aggressive surgical approach to resect the tumor is advised soon after the diagnosis of Zollinger-Ellison syndrome is established.[9]

SYMPTOMS OF ZOLLINGER-ELLISON SYNDROME

Gnawing, burning pain in the abdomen
This pain is usually located in the area between the breastbone and the navel.
Sensation of pressure, bloating, or fullness [10]
This pain usually develops 30 to 90 minutes after a meal, and is often relieved by antacids.
Pain or burning sensation in the abdomen that travels up toward the throat
Vomiting
Vomiting can include blood or coffee grounds
Diarrhea [11]
Stools may be foul smelling.
Black, tarry stools
Blood in the stools will turn them dark red or black, and make them tarry or sticky. [12]
Nausea
Fatigue
Weakness
Weight loss [13]

CAUSES:

The root cause of Zollinger-Ellison Syndrome is not known but how this syndrome develops is quite significant. This disease begins with the development of tumors in the pancreas or duodenum. There may also be tumors in the lymph nodes adjoining the pancreas. The pancreas is situated behind the stomach and is responsible for producing enzymes that help in digestion[14]. The pancreas also produces hormones which help in controlling acid formation in the stomach. The juices secreted by the pancreas, duodenum, and the liver get mixed in the duodenum[15]. This is where maximum digestion of food takes place. The tumors formed in Zollinger-Ellison Syndrome are constituted of cells that produce excessive gastrin as a result of which there is excessive gastric production in the stomach.[16] The excessive production of acid then results in formation of peptic ulcers. These tumors may at times become malignant. The growth of the tumor may be slow but the spread of the cancer in the adjoining areas like the lymph nodes or the liver may be rapid. But the sequence of events that occurs in Zollinger-Ellison syndrome is clear.[17]
The syndrome begins when a tumor (gastrinoma) or tumors form in your pancreas, duodenum or the lymph nodes adjacent to your pancreas.[18]

Your pancreas sits behind and below your stomach. It produces enzymes that are essential to digesting food. The pancreas also produces several hormones including insulin, a hormone that helps to control your blood glucose.[19]

Digestive juices from the pancreas, liver and gallbladder mix in the duodenum, the part of the small intestine next to your stomach. This is where digestion reaches its peak [20]

The tumors that occur with Zollinger-Ellison syndrome are made up of cells that secrete large amount of gastrin, which in turn causes the stomach to produce far too much produce acid. The excessive acid then leads to peptic ulcers & diarrhea[21]

Epidemiology
Frequency
United States statistics
Zollinger-Ellison syndrome (ZES) occurs in approximately 0.1-1% of all patients with duodenal ulcers. Its frequency of occurrence is reported to be approximately the same as insulinoma, the most common functioning pancreatic endocrine tumor.[22]

Race-, sex-, and age-related demographics
All races can be affected.

A slight male predominance exists, with a male-to-female ratio of 1.3:1.

The mean age of onset of ZES is 43 years; however, patients with multiple endocrine neoplasia-type 1 and ZES (MEN 1/ZES) present a decade earlier. Generally, a 5- to 7-year delay in diagnosis occurs. In a prospective study, fewer than 3% of patients were younger than 20 years, whereas 7% were older than 60 years at the time of disease onset[23].

International statistics

Incidence is 1-3 cases per million patients per year in Sweden, 0.5 cases per million patients per year in Ireland, and 0.1-0.2 cases per million patients per year in Denmark.[24]

HISTORY

PRESENTATION:

A high index of clinical awareness is needed to make a diagnosis of Zollinger-Ellison syndrome (ZES).[25]

Abdominal pain is the most common symptom, present in 75% of patients. Typically, it is located in the upper abdomen and mimics that of peptic ulcer disease. This symptom is reported more frequently by men and patients with the sporadic form of ZES.[26]

Of patients with ZES, 73% have diarrhea; this is the most common symptom in patients who have multiple endocrine neoplasia-type 1 and ZES (MEN 1/ZES) as well as in female patients [27]. The combination of diarrhea and abdominal pain is present in more than half the patients.[28]

Heartburn is the third most common symptom, and this symptom mimics gastroesophageal reflux disease (GERD).[29]

Physical

The findings of the physical examination may be normal. Note the following:

Patients may be pale if they present with gastrointestinal bleeding.[30]

Jaundice may occur if the tumor compresses the common bile duct, although this presentation is very rare.[31]

Epigastric tenderness may be present.

Other symptoms include nausea, vomiting, gastrointestinal bleeding, and weight loss. Gastrointestinal bleeding frequently is due to ulceration in the duodenum and is the presenting symptom in 25% of patients. [32]

Diagnosis of Zollinger Ellison Syndrome:

Imaging Studies:

Somatostatin receptor scintigraphy:

primary Somatostatin receptor scintigraphy (SRS) is the most sensitive imaging modality for detection of or metastatic lesions in Zollinger-Ellison syndrome (ZES); thus, is the imaging modality of choice in ZES.[33]

Computed tomography scanning

Computed tomography (CT) scanning can be performed to localize the tumor and is useful for evaluation for metastatic disease. However, its sensitivity for primary tumor localization is only 50%, and frequently, tumors smaller than 1 cm are missed.[34]

Other imaging studies

Magnetic resonance imaging (MRI) and abdominal ultrasonography also can be performed. However, the sensitivity of these modalities is lower than that of CT scanning and SRS.

Endoscopic ultrasonography is one of the newer methods for localizing gastrinomas. Its sensitivity is higher for pancreatic gastrinoma (40-75%) than for duodenal gastrinoma (50%).[35]

Pentetreotide imaging plus abdomen scintigrams.

Pentetreotide imaging plus abdomen scintigrams. The patient was asked to drink a mouthful of water with Tc-99m pertechnetate added. Dual-isotope planar images were acquired simultaneously, centering on the In-111 pho-to peaks and on the Tc-99m photo peak. The Tc-99m abdo-men images were displayed to be the background maps (A and B). The In-111 image was superimposed onto a Tc-99m image (C and D), which showed that the pathologic focus was next to the duodenum and inside the gastrinoma triangle.[36]

Barium X-ray.

The patient drinks a liquid that contains barium, which will coat the walls of the esophagus, stomach, and duodenum.[37] X-rays are then taken. The doctor will then view Your doctor will base a diagnosis on the following:

Medical history. Your doctor will ask about your signs and symptoms and review your medical history.[38]

Blood tests. A sample of your blood is analyzed to see whether you have elevated gastrin levels. While elevated gastrin may indicate tumors in your pancreas or duodenum, it also can be caused by other conditions. For example, gastrin may also be elevated if your stomach isn't making acid, or you're taking acid-reducing medications, such as proton pump inhibitors.[39]

You need to fast before this test and may need to stop taking any acid-reducing medications

to get the most accurate measure of your gastrin levels. Because gastrin levels can fluctuate, this test may be repeated a few times.
Your doctor may also perform a secretin stimulation test. For this test, your doctor measures your gastrin levels, gives you an injection of the hormone secretin and measures gastrin levels again. If you have Zollinger-Ellison, your gastrin levels will increase even more.
It's also possible to remove a tissue sample through the endoscope. You'll need to fast after midnight the night before this test, and you'll be sedated during the test[40]
X-rays, looking for signs of ulcers.

Upper endoscopy.
The doctor examines the inside of the esophagus, stomach, and duodenum with an instrument called an endoscope, a thin flexible lighted tube with a lens.
The endoscope is inserted through the mouth and down the throat, and into the stomach and duodenum. The doctor can look for ulcers, and can also remove a tissue sample, called a biopsy, for examination in the laboratory to identify if there is the presence of gastrin-producing tumors[41].

Imaging techniques.
A doctor may use a computerized tomography (CT) scan, a magnetic resonance imaging (MRI) scan, and ultrasound, or a nuclear scan in an effort to pinpoint where tumors may be located.
A **CT scan** is a diagnostic test that uses X-rays with aided by computer technology. The X-ray beams are taken from many different angles to create cross-sectional images of the patient's body. Then a computer assembles these images into a three-dimensional picture that can display organs, bones, and tissues in great detail.[42]
With the **MRI scan**, magnetic signals are used rather than X-rays to create images of the human body. These images show the differences between types of tissues.
An **ultrasound** sends out high-frequency sound waves which go into the area being examined and bounce back when they hit an organ. This is processed by a computer, which produces a map of the area being scanned.[43]
With the **nuclear scan**, radioactive substances are introduced into the body that permit a gamma camera to detect tumors.

GASTRIC OUTLET OBSTRUCTION:
Gastric outlet obstruction (GOO, also known as pyloric obstruction) is not a single entity; it is the clinical and pathophysiological consequence of any disease process that produces a mechanical impediment to gastric emptying.
Clinical entities that can result in GOO generally are categorized into two well-defined groups of causes: benign and malignant. This classification facilitates discussion of management and treatment. In the past, when peptic ulcer disease (PUD) was more prevalent, benign causes were the most common; however, one review showed that only 37% of patients with GOO have benign disease and the remaining patients have obstruction secondary to malignancy [44].

Treatment of Zollinger-Ellison Syndrome
The treatment of Zollinger-Ellison syndrome focuses on two areas: Treating the tumors and treating the ulcers.[45]
Surgery is often performed if there is only one tumor. If tumors are in the liver, a surgeon will remove as much of a liver tumor as possible (debulking).
When surgery on tumors isn't possible, other treatments are used
Attempting to destroy the tumor by cutting off the blood supply (embolization).[46]
Attempting to destroy cancer cells by using an electric current (radio-frequency ablation).
Injecting drugs into the tumor to relieve cancer symptoms.
Using chemotherapy to try to slow tumor growth.[47]

Medical Care
The goals of treatment in patients with Zollinger-Ellison syndrome (ZES) are medical control of gastric acid hypersecretion and surgical resection of the tumor. Inpatient care is aimed at first controlling the gastric acid hypersecretion. Once gastric acid hypersecretion is controlled, imaging studies

should be obtained to localize the tumor and determine tumor extent.

If the patient is acutely ill, immediate control of gastric acid hypersecretion can be achieved with intravenous proton pump inhibitors.[48] Previously, this was accomplished with histamine 2 (H2) receptor blockers. Intravenous pantoprazole was approved recently by the US Food and Drug Administration. Proton pump inhibitors are superior to H2 blockers for the control of gastric acid hypersecretion.

Patients who are candidates for surgical resection should be referred for resection of the tumor.For patients with metastatic disease, chemotherapy, interferon, and octreotide may be helpful. The response to these agents in most studies has been low. Liver transplantation for hepatic metastasis also has been reported. For patients with a single confined liver metastatic lesion, surgical resection may be attempted.[49]

Surgical Care

All patients with sporadic Zollinger-Ellison syndrome (ZES) without hepatic metastases or medical contraindications to surgery are advised to undergo surgical resection of the tumor because this decreases the risk of developing liver metastases, which can decrease the survival of these patients.

The role and timing of surgical resection in patients with multiple endocrine neoplasia-type 1 (MEN 1) is less clear. An attempt at surgical resection has been recommended if the tumor is larger than 2.5 cm. Cure is rarely achieved by surgical resection in patients with MEN 1; however, it may reduce the risk of subsequent metastatic disease.[50]

In a single-institution retrospective study with a median follow-up of 18 years from the time of the diagnosis of ZES, Mortellaro et al examined the long-term outcomes in 12 patients with MEN 1 and ZES from 1970 to the present. [1] The pancreas (n = 10), duodenum (n = 4), lymph nodes (n = 3), and liver (n = 1) were the most commonly identified gastrinoma sites. A total of 15 celiotomies were performed, and surgeries included 4 each of distal pancreatectomies and acid-reducing procedures, 3 each of enucleation of pancreatic gastrinoma and duodenal resection, 1 pancreaticoduodenectomy, and 7 noted as other. [1] There was 1 each of a patient with transient (3 y) biochemical postsurgical cure and liver metastasis of gastrinoma (but no deaths from metastatic gastrinoma).

Deaths included causes such as respiratory arrest (n = 1), possibly due to aspiration or pulmonary embolus, and nondisease related (n = 3). At the last follow-up, 7 patients were alive. The investigators observed patients with MEN 1 and ZES rarely achieve biochemical cures with surgery; however, extended surgical resection was not only not needed in resection of localized gastrinomas, but it was also associated with excellent long-term outcomes. [51]

Because gastrinoma is a rare tumor, surgical resection should be attempted only at centers with personnel experienced in treating affected patient.

Proton pump inhibitors

Class Summary

Drugs of choice in ZES. Inhibit gastric acid secretion by inhibition of the H^+/K^+/ATP-ase enzyme system in the gastric parietal cells.

-Omeprazole (Prilosec)

Decreases gastric acid secretion by inhibiting parietal cell H^+/K^+ ATP pump. Aim of therapy is to maintain BAO < 10 mmol 1 h prior to next dose.

-Lansoprazole (Prevacid)

Decreases gastric acid secretion by inhibiting parietal cell H^+/K^+ ATP pump. Aim of therapy is to maintain BAO < 10 mmol 1 h prior to next dose.

-Pantoprazole (Protonix)

Decreases gastric acid secretion by inhibiting parietal cell H^+/K^+ ATP pump. Aim of therapy is to maintain BAO < 10 mmol 1 h prior to next dose.

-Esomeprazole magnesium (Nexium)

S-isomer of omeprazole used for symptomatic GERD. Inhibits gastric acid secretion by

inhibiting H^+/K^+ ATP pump at secretory surface of gastric parietal cells.

-Rabeprazole sodium (Aciphex)
Decreases gastric acid secretion by inhibiting the parietal cell H^+/K^+ ATP pump. For short-term (4-8 wk) treatment and relief of symptomatic erosive or ulcerative GERD. In patients not healed after 8 wk, consider an additional 8-wk course.[52]

Prescription Only / Over the Counter
Rx-prescrtion only
OTC over the counter
OTC/Rx over the counter or prescription

PREGNANCY
A- Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)

B- Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

C- Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use in pregnant women despite potential risks.

D- There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use in pregnant women despite potential risks[53]

X- Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use in pregnant women clearly outweigh potential benefits.

N- FDA has not classified the drug
Controlled Substances Act Schedule

1- Has a high potential for abuse. Has no currently accepted medical use in treatment in the United States. There is a lack of accepted safety for use under medical supervision.
2- Has a high potential for abuse. Has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. Abuse may lead to severe psychological or physical dependence.
3- Has a potential for abuse less than those in schedules 1 and 2. Has a currently accepted medical use in treatment in the United States. Abuse may lead to moderate or low physical dependence or high psychological dependence.
4- Has a low potential for abuse relative to those in schedule 3. It has a currently accepted medical use in treatment in the United States. Abuse may lead to limited physical dependence or psychological dependence relative to those in schedule 3
5- Has a low potential for abuse relative to those in schedule 4. Has a currently accepted medical use in treatment in the United States. Abuse may lead to limited physical dependence or psychological dependence relative to those in schedule 4.[54]
ALCOHOL
X- Interacts with Alcohol.

HOMEOPATHIC TREATMENT OF ZOLLINGER ELLISON SYNDROME
Homoeopathy is Which form of treatment offers time-tested remedies for different diseases like Zollinger-Ellison Syndrome(ZES). It takes into account the cause and nature of the illness and Their presentation in the patient. Treatment is started after careful study, analysis and evaluation of symptoms.

Homoeopathic physician studies the case first and asks specific details about the cause and character of the disease. The further step is to find a suitable remedy Which matches the symptoms. Homoeopathic Doctor treats different People with different remedies as Their personalities are different

Homeopathic Treatment is preferred as it offers relief from Zollinger-Ellison Syndrome(ZES) without any side-effects.

'Acute Remedies' are Given to combat sudden, acute attacks and episodes brief. 'Constitutional Remedies' remedies are selected upon the patient's genetic make-up and mind, personality and lifestyle. 'Interrcurrent Remedies' Which are Given remedies are if there is no further improvement in symptoms. Homeopathic medicines treat causative factors of Zollinger-Ellison Syndrome(ZES) like high stomach acid production, gastric Tumours, etc. Hence it, symptoms like burning in stomach, nausea, and vomiting are controlled Effectively Zollinger-Ellison Syndrome(ZES) is good Brought under Control During The Earlier stages. Homeopathy is very effective in treating SEZs as it removes the symptoms from ITS roots

Homoeopathic Medicines taken Regularly Along With dietary Changes produces full relief. Quickly They are absorbed into the system and are without any side-effects and are not habit-forming. They Should be taken only after consultation from a homoeopathic doctor.[55]

AYURVEDIC TREATMENT FOR ZOLLINGER ELLISON SYNDROME

Ayurveda is the ancient Indian healing process associated with treating conditions and diseases with natural herbs and meditation. Known as the study of life and science, Ayurveda is based on the concept of Tridosha, which classifies people, diseases and remedies into three categories: Vata (air), Kapha (water or mucous) and Pitta (fire).

According to the Zollinger-Ellison Syndrome organization website, Ayurveda may be helpful in treating the symptoms of gastro-intestinal target ulcers and pancreatic and duodenal tumors associated with this condition. It lists Ayurvedic drugs such as Praval-bhasma, Shankh-bhasma and Kamdudha-Ras as treatments for stomach acid production and intestinal ulcers. Herbal medications such as Haritaki (Terminalis chebula), sunthi (Zinzibar officinalis) and Bhrungraj (Eclipta alba) are also listed in the treatment of these symptoms. For diarrhea, Kutaj-Parpati is listed as a treatment, and for bleeding associated with stomach and intestinal ulcers, it lists Vasa (Adhatoda vasaka). Stress associated with Zollinger-Ellison Syndrome can be treated with jatamansi (Nardostachys jatamansi), and tumors in your pancreas or duodenum can be treated with drugs such as Maha-Manjishtadi-Qadha[56].

Treatments for this condition include medicine to reduce the acid and surgery to remove tumors. Ayurveda may be helpful in treating the symptoms of gastro-intestinal target ulcers and pancreatic and duodenal tumors associated with this condition.

Ayurvedic drugs such as **Praval-bhasma, Shankh-bhasma** and **Kamdudha-Ras** as treatments for stomach acid production and intestinal ulcers.

Herbal medications such as **Haritaki (Terminalis chebula), sunthi (Zinzibar officinalis)** and **Bhrungraj (Eclipta alba)** are also listed in the treatment of these symptoms.

For diarrhea, **Kutaj-Parpati** is listed as a treatment.

For bleeding associated with stomach and intestinal ulcers **Vasa (Adhatoda vasaka)** is used.

Stress associated with Zollinger-Ellison Syndrome can be treated with **jatamansi (Nardostachys jatamansi).[57]**

RADIOLOGY AND ZOLLINGER ELLISON SYNDROME:

Zollinger-Ellison syndrome (**ZES**) is a clinical syndrome that occurs secondary to a gastrinoma.

CLINICAL PRESENTATION

Diagnosis of ZES is often delayed by 5-7 years after the onset of symptoms .

Pathology

Gastrinomas are usually multiple and typically located in the duodenum (more common) or pancreas (less common). These tumours secrete gastrin that results in hypersecretion of gastric acid, which in turn results in diarrhoea, gastritis, severe gastro-oesophageal reflux disease and peptic ulcer disease .

Markers

increased gastrin levels in fasting patients (but not specific, and some data suggest that clinical assays may be unreliable .

Associations

multiple endocrine neoplasia (MEN) type 1: ZES occurs when gastrinoma is functional
Radiographic features
Fluoroscopy
On double-contrast upper gastrointestinal studies the following features may be seen :
thickened rugal folds
multinodular gastric contour
erosions and ulcers, especially in atypical locations
barium may be diluted by the high volume of fluid in the stomach

CT
negative contrast may be used to distend the stomach
thickened rugal folds
multiple gastric nodules/masses
Treatment and prognosis
Surgery plays a vital role . Death from complications of ZES (e.g. perforation, haemorrhage) can occur.

History and etymology
It is named after **Robert M. Zollinger** and **Edwin H. Ellison**, who in April 1956 described two cases of severe, multifocal ulcerative lesions of the proximal gastrointestinal tract, which were remittent, refractory to surgery and associated with tumours in the adjacent pancreas .
Differential diagnosis
Possible differential considerations include:
Gastritis from other causes, e.g. *H. pylori* infection, hypertrophic gastritis,
Gastric lymphoma

STREPTOZOCIN AND ZOLLINGER ELLISON SYNDROME

Chemotherapy for malignant Zollinger-Ellison tumors: successful treatment with streptozocin and fluorouracil.
Streptozocin is of value in the treatment of malignant insulinomas, but has not previously been shown to be effective against Zollinger-Ellison tumors, which secrete gastrin. This patient's malignant gastrinoma responded to treatment with streptozocin and fluorouracil. Tumor regression was verified by the disappearance of the epigastric mass, improvement of liver function, and reduction of serum gastrin levels to one third of the pretreatment level. The patient has been in remission for more than two years and has had no further treatment since the first year.[58]
An evaluation of human recombinant alpha interferon in patients with metastatic gastrinoma.

BACKGROUND:
Metastatic gastrinoma is becoming increasingly recognized in patients with Zollinger-Ellison Syndrome. The mean 5-year survival of these patients is < 20%. Chemotherapeutic regimens are of limited benefit. The aim of this study was to evaluate the use of interferon in these patients because a preliminary report suggested it might be effective.

METHODS:
The efficacy and toxicity of interferon was assessed in 13 consecutive Zollinger-Ellison syndrome patients with liver metastases. Patients were treated with human recombinant alpha interferon (5 million IU, subcutaneously [SC]) daily and followed up at 3-month intervals with multiple imaging studies. At each follow-up, toxicity of therapy was assessed and fasting serum gastrin concentrations were obtained.

RESULTS:
No patient showed a reduction in tumor size at any follow-up. One patient died after 2 months. At 6 months, six patients (46%) had stable tumor size in the liver, although new bone metastases developed in one patient. Three patients showed stable disease for up to 21 months. Changes in serum gastrin correlated with tumor response at 6 months. All patients developed some side effects of therapy. Thirty-one percent required dose reduction, and one patient (8%) had to have interferon therapy interrupted briefly.

Results:
These results fail to define a therapeutic role for interferon in the treatment of metastatic gastrinoma.[59]

Acupuncture and Acupressure Treatment of Zollinger Ellison Syndrome**:**

Different Allopathic Medications Associated With Zollinger Ellison Syndrome
Proton Pump Inhibitors

DRUG NAME	RX/OTC	PREG	CSA	ALCOHOL
Prontix (Pantoprazole systemic)	RX	B	N	
Nexium (Esomeprazole systemic)	RX	C	N	
Omeprazole	RX/OTC	C	N	
Prevecid (Lansoprazole systemic)	RX/OTC	B	N	
Rabeprazole Systemic	RX	B	N	
Prilosec (Omeprazole systemic)	RX	C	N	
Aciphex (Rabeprazole systemic)	RX/OTC	B	N	

H2 Antagonists:

Drug name	Rx/OTC	Preg	CSA	Alcohol
Famotidine systemic	RX/OTC	B	N	
Zantac (Ranitidine systemic)	RX/OTC	B	N	
Cimetidine Systemic	RX/OTC	B	N	x
Pepcid AC(Famotidine systemic)	OTC	B	N	
Tagamet HB(Cimetidine systemic)	RX/OTC	B	N	x
Deprizine(Ranitidine systemic)	RX/OTC	B	N	
Careone Acid Reducer(Rantidine)	RX/OTC	B	N	

Antacids

Drug Name	Rx/OTC	Preg	CSA	Alcohol
Aluminium hydroxide systemic.				
Alternagel (aluminium hydroxide systemic).				
Aluminium hydroxide/ magnesium hydroxide.				

Acupuncture relieves by improving the physiological function of the organs and organ system. In acupuncture therapist will first diagnose the case on the basis of energy system or chi blockage as well. as on the basis of status of five elements. On this basis certain disease specific acupoints are selected and stimulated

Psychotherapy and Hypnotherapy Treatment of Zollinger Ellison Syndrome
Psychotherapy and hypnotherapy can help in stress relief. They can help in better coping and early relief.[60]

EMERGENCY THERAPIES FOR ZOLLINGER ELLISON SYNDROME

Interferon alfa

Limited research has demonstrated a potential benefit of combining interferon alfa with somatostatin analogs. Further research is required to justify the use of this combination with somatostatin analogs.

Netazepide

Netazepide is a gastrin/cholecystokinin (CCK)-2 receptor antagonist that is currently being investigated as a potential treatment for the type of gastric carcinoids that develop in patients with atrophic gastritis, and for gastric carcinoids associated with the presence of multiple endocrine neoplasia (MEN) type 1 and Zollinger-Ellison syndrome.[61]

Peptide receptor radionuclide therapy (PRRT)

Peptide receptor radionuclide therapy (PRRT) is an emerging treatment that combines octreotide with a radionuclide and is currently undergoing investigational studies. Three radionuclides are used: indium 111 (111In), yttrium 90 (90Y), and lutetium 177 (177Lu). These radiopeptides are specifically targeted to NETs and destroy tumor cells by radioactive emission with gamma- and/or beta-radiation. The results of PRRT with 177Lu show a decrease in tumor size, a decrease in symptoms, and a halt in tumor progression. Side effects of PRRT therapy include renal failure rarely, but more commonly nausea, vomiting, and abdominal pain. PRRT should be considered for patients with tumors visualized by somatostatin receptor scintigraphy (SRS) or Ga-68 DOTATATE PET/CT and not responsive to current treatments[62]

CONCLUSION:

Though PPIs offer value and relief to many people, they are not universally beneficial. In fact, a study by the San Francisco Department of Public Health estimated that only 30 to 40 percent of PPI users actually require the medications. The remaining 60 to 70 percent of patients should instead try lifestyle changes and antacids.

In addition, researchers have conducted a number of studies on the side effects and complications of PPI use, including kidney failure, heart attack, dementia and more.

There has been a grave association made between PPIs and cognitive decline. In 2011, a group of German physicians and researchers concluded a seven-year study involving 73,679 elderly persons, all of whom were free of dementia at the start of the study. Approximately 3,000 of the subjects were regular users of PPIs. The researchers found that the PPI users had a significantly increased risk of dementia.

Additionally, there is a link between PPIs and kidney disease and kidney injury. A group of Canadian researchers reviewed nine years of medical records of 290,592 people, and discovered that PPI users were more likely suffer from acute kidney injury than non-PPI users. Also, in 2016, the Journal of the American Medical Association released a report showing that PPI users were much more likely to experience chronic kidney failure.

The Stanford School of Medicine conducted a study involving the health records of 3 million Americans, a portion of which were PPI users. Researchers found that there is an association between usage of PPIs and heart attacks, and showed a 20 percent increase in risk of heart attack after using these medications.

Infection is more common in those who use PPIs. Researchers in Denmark found that PPI users were 50 percent more likely to acquire pneumonia while in a hospital.

The University of Maryland reported that certain PPIs (Prevacid, Nexium, and Prilosec and its generics) can increase the risk of bone breaks in people who use the medications for more than one year. Specifically, the bones that are prone to breaking due to PPI use are those within the wrists, hips, vertebrae and forearms and hence Ayurvedic medications are compared better than allopathic(proton pump inhibitors) for treatment of Zollinger Ellison syndrome.

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