Methods on employed in screening of antiulcer drugs - an overview

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INTRODUCTION

Peptic ulcer disease is a group of disorders characterized by the presence of ulcers in any portion of gastrointestinal tract (GIT) exposed to Acid in sufficient concentration and duration [1]. Imbalance occurs between aggressive factors like acid and pepsin secretion. The drug treatment of peptic ulcer has significantly brought down the morbidity and mortality and need of surgical interventions which may be attributed to the advent of H2 blockers and proton pump inhibitors. These symptoms frequently occur several hours following a meal, after the food leaves the stomach but while acid production is still high. Instead of pain, some patients experience intense hunger or bloating. Many animal models are using to induce ulcer to identify the antiulcer property of many new and existed drugs such as Pyloras ligated rat, Stress ulcers, Histamine induced gastric ulcers, Cysteamine induced duodenal ulcers, Dulcerozine induced duodenal ulcers, Duodenal ulcers following Infusion of pentagastrin and carbacol, Indomethacin and histamine induced duodenal ulcers, MPTP induced duodenal ulcers. The above all induced types are useful experimental model for the research.

Key words: Pyloras, Peptic ulcer, Duodenal ulcer and Inflammation.

ETIOLOGY AND PATHOGENESIS OF ULCER

H. Pylori

H. Pylori is the main cause of stomach ulcers, was first identified by the two Australian scientists in 1982. H. Pylori is a gram negative bacillus, motile, microaerophilic, flagellated and spiral shaped bacteria [7]. Type I strains of H. Pylori possess a pathogenic activity, that encodes the effectors protein cytotoxin - associated gene A (cagA). After Translocation into the host cell, cagA effects cell shape, increases cell motility, disturbs cell junctional activity and thus responsible for gastric carcinomas and gastric ulcers. H. Pylori causes increases expression of cytokines such. TNF-α in gastritis. Further, IL -1 β is too overexpressed in the H. Pylori – induced gastritis. H. pylori - infected gastric
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mucosa showed infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells in the lamina propria, and intraepithelial severe neutrophil infiltration [8].

**Fig 1. Ulcer disease**

**Fig 2. Duodenal and gastric ulcer**

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**Gastric acid secretions**

Gastric acid is established as one of the major ulcerogenic factor for the induction of gastric ulcer disease. It has been reported that about 50% of gastric ulcer patients are pepsin and acid hypersecretors. But, on the other hand, gastric acid plays a stringent role in gastric defense. It is the first line of mucosal defense to prevent bacterial colonization and reduced their ability to entrance in the mucosal layer. Acid secretion is suggested to be stimulated by three principle secretagogues histamine, acetylcholine and gastrin. Gastrin stimulates acid secretion either by direct stimulation of parietal cells or by the release of histamine from ECL cells [9].

**DIAGNOSIS**

The history and physical examination are important to identify patients at risk of ulcer, perforation, bleeding, or malignancy. However, a systematic review of models using risk factors, history, and symptoms found that they did not reliably distinguish between functional dyspepsia and organic disease. Therefore, the test-and-treat strategy for H. pylori is recommended for patients with dyspepsia who have no alarm symptoms. The American College of Gastroenterology (ACG) recommends testing for H. pylori infection in patients with active PUD or history of PUD, dyspepsia symptoms, or gastric MALT lymphoma. The rationale for testing patients with a history of PUD who are currently asymptomatic is that detecting and treating H. pylori infection can reduce the risk of recurrence [10]. The test-and-treat strategy for detecting H. pylori is appropriate in patients with dyspepsia and low risk of gastric cancer age younger than 55 years and no alarm symptoms such as unexplained weight loss, progressive dysphagia, odynophagre current vomiting, family history of gastrointestinal cancer, overt gastrointestinal bleeding, abdominal mass, iron deficiency anemia, or jaundice. Endoscopy is recommended for patients who are 55 years or older, or who have alarm symptoms [11].

**INDUCING METHODS**

**Gastric ulcers**

**Pylorus ligated [shay] rat**

This is perhaps the oldest animal model of gastric ulcers developed by shay et al. Albino rats weighing 150–200 g are housed in individual cages and fasted for 24–36 hours prior to pyloric ligation. Care being taken to avoid coprophagy. Under light ether anaesthesia the abdomen is opened by a small midline incision below the xiphoid process, pyloric portion of the stomach is slightly lifted out and...
ligated avoiding traction to the pylorus or damage to its blood supply. The stomach is replaced carefully and abdominal wall closed by interrupted sutures. The drugs are administered subcutaneously immediately after pyloric ligation. The animals are deprived of both food and water during the postoperative period and are sacrificed at the end of 19 hours after operation. Stomachs are dissected out, contents are drained into tubes and subjected to analysis for pH and free and total acidity. The stomachs are then cut open along the greater curvature and the inner surface is examined for ulceration. The ulcer index is calculated. Usually circular lesions are observed. Many times lesions and petechiae are also seen. The method has great predictive value for antiulcer agents in the human disease though, the ulcers in this model are localized in the rumenal area of the stomach whereas in the human disease the glandular stomach and duodenal region are most commonly involved.

**Stress ulcers**

Gastrointestinal erosion is the one of the consistent finding in man and in experimental animals subjected to different types of stress. These ulcers appear to be the experimental counterpart of Curling’s ulcer or human stress ulcers. The major advantage of these preparations over pyloric ligated are that they are technically simple, they do not require anaesthesia or surgery, they bring central nervous system into play and the lesions produced by these methods are located in the glandular region of the rat stomach. The following methods have been commonly used [12].

**Restraint ulcers**

The method described by Brodie and Hanson is used for the production of restraint ulcers. Albino rats of either sex weighing 150-200 g are housed in separate cages and divided into groups. The animals are deprived of food for 36 hours before experimentation. Each rat is then placed in a piece of galvanized steel window screen of appropriate size. The screen is moulded around the animal and held in a place with staples. The limbs are put together and tightened with adhesive tape so that the animals cannot move. The drugs under investigation are administered 30 min before subjecting the animal to restraint. At the end of 24 hours period the animals are removed from the screen and killed using overdose of ether. The stomach is opened along the greater curvature, wasted with tap water and the ulcers are examined and scored by a suitable method. In one of the methods total areas of stomach mucosa and that of ulcers are noted for determining the ulcer index. For this purpose the stomach is removed from the body, opened along the greater curvature cleaned and spread on card board with the mucous surface upwards avoiding corrugation. Tracing paper is placed over the stomach and the outline of stomach and the areas of erosions of ulceration are traced on it. This method has been successfully used for studying the healing of ulcers as well. In a series of similar investigations Brodie and coworkers systemically examined the restraint technique and popularized its use North America concluded that the technique was a useful one but that several disadvantages were still present, including the fact that the lesions did not penetrate the muscularis mucosa and as such were not ulcers in true sense and the fact that the technique appeared to be somewhat species specific. Hence the restraint method has been modified by various workers in order to make it less time consuming, less cumbersome and more reproducible. This method has been excellently reviewed by Glavin. Some of the commonly used modifications are described here [13].

**Water immersion induced restraint ulcers**

It has been shown that exposure of rats to restraint stress significantly decreases gastric acid secretion but there occurs an increase in gastric acid secretion towards the restress level for a few hours when the restraint animals are subjected to additional water immersion. Since the development of gastric lesions during stress significantly enhanced by exposure to water immersion, the rise in acid secretion may be important in the aggravating process of lesions during water immersion. In this method male wistar rats, fasted for 24 h are immobilized in a stress cage and then immersed to the level of xiphoid process in a water bath (23°C) for 16 h. The animals are sacrificed by a blow on the head, each stomach is removed, filled with 1% formalin and then put into it for 10 min. the ulcer index can be estimated by measuring the total length of the lesions and the test drugs are administered 30 min prior to stress [14].

**Cold and restraint ulcer**
In 1977 Vincent et al devised a method of restraining animals which did not require an extensive period of starvation prior to use. Did not require that the animals be restraint for lengthy periods of time, restricted virtually all the movements of animals without respiratory or circulatory trauma and rapidly produced very high and very reliable degree of gastric glandular restraint ulcer in rodents. This model, later referred to as hypothermic restraint ulcer, represents a useful experimental ulcer model and a valuable research tool for use by psychologists and pharmacologists in examining the cause course, consequence and treatment of peptic ulcer disease. In this method wistar rats are deprived of food for 12 hours. They are then immobilized in a stress cage and forced to remain in a cold room (4° - 6°C) for 3 hours. The animals are sacrificed by a blow on the head and the ulcer index is calculated as described for restraint ulcers. The test drugs are administered 30 min before immobilizing the animals. Gastric erosion following short term stress and concurrent administration of nonsteroidal anti-inflammatory drugs [15].

**Restraint + aspirin ulcers**

Male wister rats are deprived of food for 24 -36 hours. Aspirin (50 mg/kg PO) in 1% CMC is administered 30 min before restraint. The test drugs are given 1 hour before the restraint. The rats are subjected to restraint by placing them individually in a piece of galvanized steel window screen which is moulded tightly around and held with adhesive tapes so that the animals cannot move. After 6 hours the animals are removed from the screen, sacrificed and the intensity of gastric lesions determined.

**E.Swimming stress ulcer**

Male wister rats fasted for 24-36 hours are forced to swim inside the vertical cylinders (height 30 cm, diameter 15 cm) containing water up to 15 cm height maintained at 23° C. three hours after the stress, they are removed from the cylinders and sacrificed by a blow on the head. The ulcer index is determined as described by Weisher and Thiemer. The test drugs are administered 30 min prior to stress. Activity stress ulcers in rats If young adult rats are individually housed in running wheel activity cage allowing continuous access to the wheel, and fed only one hour each day, some of this animals will die within 4-16 days. An interesting feature of this phenomenon is that rats, demonstrating high activity levels which die, reveal extensive lesions in the glandular stomach. Since these glandular lesions resembled the “stress ulcer” reported by other workers and since the activity was shown to be instrumental in their development, these lesions have been designed as activity stress ulcer. The method has been described in detail by Pare and is of limited value in the evaluated of antiulcer activity of new drugs as it is time consuming and needs continuous supervision of the animals in the activity cages. Interestingly, animals developing activity stress gastric lesions are hypo-secretors of gastric acid and do not respond to histamine H2 blockers. Activity stress gastric lesions are, however, reduced by centrally acting agents such as diazepam and imipramine suggesting that an aberration in central neurotransmission plays a role in their development. However, some local factors also contribute to activity-Stress gastric damage [16].

**Haemorrhagic shock induced gastric ulcers**

Bleeding acute gastric erosions have now become the second most common cause of upper gastrointestinal haemorrhage. The increased use of alcohol, NSAIDs, as well as the increased incidence of major trauma, burns and surgery, has resulted in a great increase in the frequency of gastric erosions. The understanding of the pathogenesis of these erosions has been hampered by the lack of a suitable experimental model. In order to investigate the relationship between haemorrhagic shock and acute gastric erosions rats are anaesthetised with i.p. urethane (125 mg/ 100g). After 20-30 min of stabilization and baseline measurements, 13 ml/kg of blood is removed every 1-2 min, from a cannula inserted into the carotid artery, producing hypotension to a mean arterial line to monitor the arterial blood pressure. Twenty minutes after the shock, the animals are killed, the stomachs are removed and the intensity of the macroscopic lesions is graded by a suitable method.

**Histamine induced gastric ulcer**

Induction of experimental gastric ulcers in several species by histamine administration has long been recognized and is mediated through both enhanced gastric acid secretion and vasopastic action of histamine. In guinea pigs histamine produces gastric ulceration in 100% animals along with increased volume of gastric secretion and marked
enhancement of free total acidity. The percentage of area of ulceration and its intensity are reproducible and the model provides another species for studying the antiulcer and anti-secretory activities of novel compounds. Male guinea pigs weighing 300-40 g are fasted for 36 hours (water allowed). Gastric ulceration is induced by injection 1 ml of histamine acid phosphate (50 mg base) i.p. 15 min before and 15 min after histamine to protect the animals against histamine toxicity. The drugs under investigation are given p.o or s.c. 30-45 min before histamine injection. The animals are sacrificed four hours after histamine administration and the stomach is dissected out. The gastric contents are subjected to analysis and the stomach is cut open and the degree of ulceration is graded according to the method of Barret.

Acetic acid induced chronic gastric ulcer

The various problems relating to human peptic ulcer disease one of the least understood aspects is the chronicity of the disease. A number of models of chronic astringent ulceration have been trierusing submucosal injection of silver nitrate, formalin, nicotine and epinephrine in cats and dogs etaslesionsgrossly and histologically resembled human gastric ulcer, however they healed aidly and completely within two to three weeks. Two simple methods for theproduction of clearly defined, deep, gastric and duodenal ulcers in rats have been described by Okabe and Pfeiffer. These methods have been successfully used by a number of workers to screen newer anti-ulcer agents [17].

Gastric mucosal damage by NSAIDs

Aspirin

Aspirin is suspended in 1% carboxy methyl cellulose in water (20 mg/ml) and aministered orally (gavage) in a dose of 500 mg/kg in 36 hours fasted rats four hours later the animals are sacrificed. The stomachs are removed and open along the greater curvature to determine the ulcer index. Ulcer index is measured by the method of Ganguly and Bhatnagar. Each lesion is measured along its greatest length. In case of petechiae, five of these are considered to be equivalent to 1 mm of ulcer. The total area of stomach mucosa and that of the ulcer mucosa are noted for determining the index. Gastric lesions induced by this drug are multiple in each stomach. They are evaluated singly according to their dimensions and severity which is indicated by area of stomach divided by the area of ulceration in mm2 scale. The administration of aspirin results in the production of gastric mucosal damage mainly in the glandular segment of the stomach in 100% of the animals. The majority of the gastric lesions are gastric erosions i.e. superficial mucosal lesions not penetrating the musculis mucosa. Based on the concept of gastric irritancy test adapted by Goburdhan have introduced a new method for the product of mean ulcer index defined as the mean gastric irritancy index which is the product of mean ulcer number and mean gastric irritancy size. This index provides sample scope for studying the dose dependent ulcergenecity of NSAIDs as well the effect of gastroprotective agent.

Phenebutazone

This is given in a similar fashion as aspirin in a dose of 100 mg/kg. Two doses are given at an interval of 15 hours and 6 h after the second dose the animals are sacrificed and assessed for the gastric mucosal damage. The drugs for studying atro-protective effects are administered 30 min before each dose of phenebutazone.

Indomethacin and Ibuorofen

These are also adminstraon a similar fashion. Indomethacin is given in a dose of 10 mg/kg. While ibuprofen is given in two doses of 200 mg/kg, p.o. at 15 hours intervals. The animals are sacrificed 6 hours after indomethacin administration and 6 hours after the second dose of ibuprofen.

Reserpine induced solitary chronic gastric ulcers

Reserpine produces severe hemorrhagic glandular ulceration of the stomach which has been attributed to significant degranulation of gastric mast cells and consequent liberation to histamine. These events are thought to be eholinergically mediated. The morphological changes in gastric mucosa are very similar to the destructive changes found in the mucosa of human gastric ulcers [18].

Serotonin induced gastricmucosal lesions

Serotonin ulcer, one of the chemically induced experimental gastric ulcers, has been described by Wilhelmi and Hedinger and Veraguth. Since then it has been widely used for the investigation of the etiology of peptic ulcer disease and as a tool in the search for new antulcer drugs. Male rats of wister strain are used for the experiments. The animals are fasted for 24 h prior to the experiments, water being provided. Serotonin creatinine sulphate is
found to induce a moderate but evident gastric lesion. In gross observation, gastric lesions are scarcely noticed at 0.5 h after serotonin injection (ulcer index 1.2), but are obviously distinguishable at 1 hr (ulcer index 7.7) and reach maximum intensity at 4 h (ulcer index 15.2). The lesions are located mainly at the side of the greater curvature of the corpus. The ulcer index decreases to 8.0 at 8 h and is maintained at this level upto 24 h after serotonin injection [19].

**Dimaprit induced gastric ulcers**

On the basis of universally recognized hypothesis about the involvement of H2 receptors with dimaprit as specific H2 receptor agonist. Dimaprit was administered 24 h fasted rats and the animals were sacrificed 4 hours after injection. The drugs for studying their gastroprotective effects were given 30 min 48 before dimaprit. The procedure is extremely simple and rapid. Its feasibly and specificity are added advantages. It is very useful for evaluating not only the absolute potency of a drug given by any route but also of other pharmacodynamic parameters particularly the length of action which seems to be an important criterion in selecting new potentially H2 antagonistic drugs.

**Endotoxin (Lipopolysaccharide) induced gastric mucosal damage**

Gastric mucosal ischemia is recognized as one of the major factors in the pathogenesis of acute gastric ulceration. Consequent to the impaired gastric blood flow during shock, the clearance of back diffusing H is reduced. The intramural pH declines and ulceration occurs. These observations based on the circulation have led to developed of another gastric ulcer model using endotoxin shock. Administration of endotoxin (20 mg/kg, i.p.) produced a moderate degree of gastric mucosal damage in rats. The lesions remained confined to the glandular mucosa and consisted of small punctiform lesions, erosions was a typical submucosal ecchymosed in the glandular stomach observed in about 30% of the animals. Pretreatment with ranitidine, pirenzepine, proglumide, sucralfate and naloxone provided significant protection.

**DUODENAL ANTI ULCER STUDIES**

**Cysteamine [mercaptamine] induced duodenal ulcers**

Cysteamine inhibits the alkaline mucus secretion from the Brunner's glands in the proximal duodenum and stimulates gastric acid secretion rate. Gastric emptying is also delayed and serum gastrin concentration is increased. Cysteamine induced duodenal ulcer resembles duodenal ulcer in man to its location, histopathology some aspects of pathophysiology. The development of duodenal ulcers in response to cysteamine is inhibited by the anticholinergic agents, antacids, prostaglandins and H2 receptor antagonists. Since multiple dosing is necessary to prevent cysteamine induced ulcers, the usefulness of the model in a screening program me is limited by the large quantity of drug required. Hence, cysteamine has also been used in mice to produce duodenal ulcers which can be used for theevaluation of anti-ulcer drugs overcoming the above mentioned draw back seen in rats. The details of dosing and frequency of administration of duodenal ulcerogens have been summarize the table ulcers develop 2 to 4 mm away from the pylorus on the anterior antimesenteric wall of the duodenum and frequently perforates or penetrates the liver. A small ulcer is usually present on the posterior wall of the duodenum, and it invariably penetrates the pancreas. The lesion appears to start in the absorptive cells of villas folds of the proximal duodenum and progresses downward, resulting in an avillas area. The eventual ulcer crater contains necrotic debris and is sharply demarcated and infiltrated by inflammatory cells by the in the thread day If perforation occurs, localized peritonitis ensues or penetration necrosis and haemorrhage are evident in the corresponding parts of the liver and/or pancreas. Granulation tissue and (in 2 to 3 weeks) dense fibrous connective tissue are seen around the ulcer, and early mucosal epithelial regeneration on the edge of the ulcer can be detected. Active ulceration is evidenced by the presence of necrotic material and acute inflammatory response on the lumenal layers of the crater. The duodenal ulceration is associated with increased gastric output, delayed gastric emptying, and elevated serum gastrin levels duodenal ulcers in rats given cysteamine and in humans have a similar pathomorphologic history and are located on the anterior and/or posterior wall frequently penetrating the pancreas. Functionally, the human duodenal ulcerationis accompanied the pancreas gastric acid output and fasted serum gastrin levels, although these correlations exist in the course of cysteamine induced duodenal ulcers as well [20].
Dulcerozine induced ulcers
Kurebayashi et al reported that acute perforating duodenal ulcers can be produced in rats following single oral administration of dulcerozine, compound structurally related to non-steroidal anti-inflammatory drugs such as henylbutazone and others known to cause gastrointestinal damage in man and animals. It has been proposed that prolonged gastric hypersecretion might be an important factor contributing to the pathogenesis of duodenal ulcer in this species. The dulcerozine induced duodenal ulcers in rats is a useful model for studying the pathogenesis of duodenal ulcer and testing the anti ulcer drugs from the practical and pathogenic standpoint because:

- The lesions develop are analogous to the clinical disease with respect to location.
- The factor producing the pathologic changes is similar in man and animal used.
- The drug treatment and a surgical operation effective in animals could be clinically useful.
- It is extremely simple to perform, the massive production is feasible and the results are obtained within 18 hours.

Dimaprit induced duodenal ulcers
Recently Del Soldato et al, have used the model of dimaprit induced duodenal ulcers in the guinea pigs to study activity of some H2 receptor antagonists. Dimaprit is injected sub cuteneously to the 24 hours fasted guinea pigs in the dose of 2 mg/kg every hour and the animals are sacrificed 1 hour following the last injection. It variably induces severe haemorrhagic ulceration primarily in the duodenal bulb which is associated with a significant increase in gastric volume and acid content. The test drugs are administered 30 min before the first dose of Dimaprit.

Duodenal ulcers following s.c. infusion of pentagastrin and carbachol
Female rats are immobilized in individual Bollman cages. Acid Secretion is stimulated by a 24 h subcutaneous infusion of 1 l/kg/min pentagastrin plus 0.5 mg/kg/min carbachol in physiological saline (0.01 ml/min). The test compounds are administered 5-10 min before beginning the subcutaneous infusion. The animals are crificed at the end of 24 h and the intensity of duodenal ulceration by a suitable grading method (Robert et al, 1970). The main drawback of this method is that the lesions are distributed over widespread areas of the duodenum and are not restricted to the proximal part of duodenum.

Indomethacin + Histamine induced ulcers
A simple administration of indomethacin and subsequent dosing with histamine consistently produces lesions at the opposite of the recentrics attachment in the proximal duodenum in rats. The physiological factors involved in this model appear to be relevant to the pathogenesis of human duodenal ulcer disease. It is a simple procedure, has a high incidence and no mortality and involves pharmacological mechanisms. It is perhaps the first model to demonstrate the duodenal ulcerogenic effect of indomethacin at a low pharmacologic dose. Indomethacin (5 mg/kg ) is first given s.c. to rats fasted for 24 h and subsequently histamine dihydrochloride (40 mg/kg) is given three times at 2.5 h intervals, beginning 30 min after the injection of indomethacin. This combined treatment induces one or two round lesions (9.8 ±1.44 mm 2) in the proximal duodenum at an incidence of 100% and few lesions in the corpus and antrum of the stomach. Indomethacin or histamine alone have no effect on either the duodenum or the stomach. The lesions in the duodenum and antrum are inhibited by oral cimetidine and 16,16 dimethylprostaglandin E 2 in a dose dependent manner, whereas those in the corpus were inhibited only by cimetidine. The detailed results indicate that the development of duodenal lesions induced by indomethacin plus histamine in rats is due to both an increase in gastric acid secretion and an impairment of acid induced duodenal HCO 3 secretion. This newly established model is expected to be useful for studying the pathogenesis of duodenal ulcers and for screening antiulcer agents.

MPTP induced ulcers
Szabo et al have shown that parkinsonism inducing agent l-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) given in multiple daily doses, either p.o. or s.c. induces solitary or double duodenal ulcers in the rat in a dose dependent manner. MPTP decreases the gastric secretion of acid and pepsin as well as pancreatic bicarbonate, trypsin and amylase. Thus it produces duodenalulcers that are possibly associated with impaired defence in the duodenal bulb (e.g. decreased availability of duodenal and pancreatic bicarbonate) However, there is very limited
experience with model as yet in order to establish its suitability for routine use in the evaluation of antiulcer drugs. Only some dopamine agonists like bromocriptine and lergotrile and monoamine oxidase inhibitors like pargyline and deprenyl have been shown to prevent MPTP induced duodenal ulcers in rats [21].

SUMMARY AND CONCLUSION
The knowledge of the pathophysiology of gastric ulcer disease remains incomplete. Current pharmacological management of gastric ulceration is directed primarily at the reduction or neutralization of gastric acid secretion despite evidence that patients with this disease often exhibit normal gastric secretory activity. Attempts have been made to prevent or reduce gastric mucosal injury by cytoprotective agents without diminishing gastric acidity [21].

A relatively new ulcerogenic procedure such Pylorasis ligated rat, Stress ulcers, Histamine induced gastric ulcers, Acetic acid induced chronic gastric ulcers, Cysteamine induced duodenal ulcers, Dulcerozine induced duodenal ulcers, Dimaprite induced duodenal ulcers, Duodenal ulcers following Infusion of pentagastrin and carbachol, Indomethacin and histamine induced duodenal ulcers, MPTP induced duodenal ulcers is described. This procedure is simple, effective and produced a reliably high incidence of gastric glandular lesions in a variety of animal species. In some cases, these lesions penetrate the muscularis mucosa and as such may be called ulcers. It is suggested that the above mentioned all types of induced models procedure meets the established criteria for a useful experimental ulcer model and thus represents a viable research tool [22, 23].

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CONFLICT OF INTEREST
No interest

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