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Review Article

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A REVIEW ON PRECLINICAL ANIMAL MODELS FOR DEVELOPMENT GASTRIC ULCERS & SCREENING OF ANTI ULCER DRUGS

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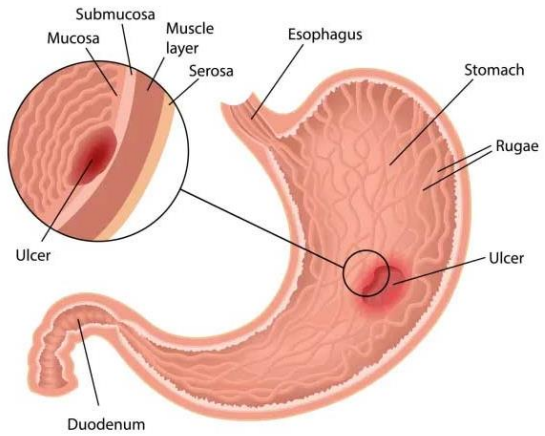
INTRODUCTION

Gastric ulcers are the severe gastrointestinal disease that will leads to severe affects. Anti-ulcer drugs such as H2 receptor antagonists, proton pump inhibitors, anticholinergics, antacids, anti H. Pylori drugs are used to reduce ulcers. The therapeutic evaluation and quality of these drugs will be established by in vivo preclinical animal model development for gastric ulcers.

Gastic Ulcers

A sore or rupture that is developed on the walls of the oesophagus, stomach, or small intestine which lead to inflammation or pain.



The aggressive factors that induce the ulcers are

- Heavy secretion the stomach acids such as HCL (Hydrochloric acid) and pepsin.
- High consumption of NSAIDS and alcohol which produce toxicity.
- Insufficient food diet.
- Stress.
- Most causative organism such as Helicobacter pylori.

Factors which help to prevent the ulcers are

- Sufficient secretion of gastric acids in the stomach.
- Prostaglandins, mucosa, nitric oxide, bicarbonates, and growth factors secretion will reduce the ulcer formation.

The ulcers can be reduced by anti-ulcer drugs. The quality of the drugs can be identified by developing the gastric ulcers in suitable animal models.

Presently available anti-ulcer drugs are as follows

1) H2 receptor antagonist: Cimetidine, Ranitidine, Famotidine
2) Proton pump inhibitors: Omeprazole, Pantoprozole, Lansoprazole
3) Anticholinergics: Pirenzepine, Telenzepine, Propanthalin
4) Prostaglandin analogues: Misoprostal , Enprostil
5) Antacids:

1. Systemic: Sodium bicarbonate
2. Non-systemic: Mg hydroxide

6) ulcer protective: Sucralfate
7) Ulcer healing drugs: Carbenoxolone sodium.
8) Anti H.pylori drugs: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, tetracycline.

Evaluation of the various anti ulcer activity and of the upcoming drugs and as well for as new drugs, these preclinical evaluation methods for gastric ulcers by invivo models are most required. This review paper focused on development and screening of various gastric ulcer models induced by different chemicals and surgical methods.

List of the in vivo models for gastric ulcer development

- ✓ Reserpine induced gastric ulcer model
- ✓ Acetic acid induced gastric ulcer model
- ✓ Diethyl dithiocarbonate induced ulcer model
- ✓ Serotonin induced gastric ulcer model
- ✓ NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) induced ulcer model
- ✓ Water-immersion stress ulcer model

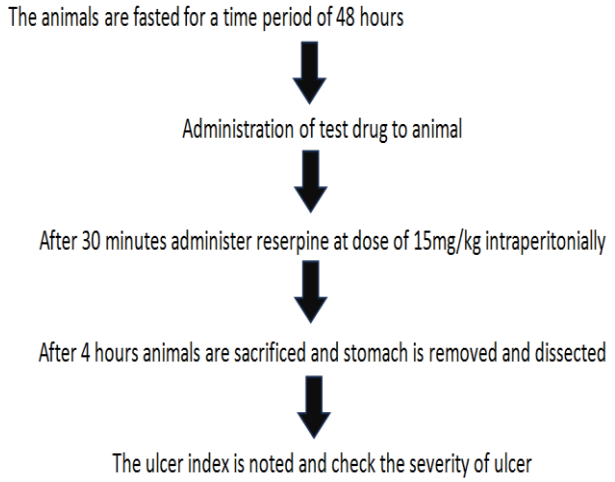
- ✓ Histamine induced gastric ulcer model
- ✓ Ethanol induced gastric ulcer model
- ✓ Pylorus ligated induced ulcer model
- ✓ Cysteamine induced ulcer model

Reserpine induced gastric ulcer model

Principle: The cholinergic system is effected by the reserpine. Degranulation of the gastric mast cells occurs by the secretion of histamine by the action of reserpine.

- ❖ Animal used: Female sprogue-Dawley rats
- ❖ Gastric ulcer induced chemical: Reserpine[15mg/kg]
- ❖ Route of administration: Intraperitonially

Procedure

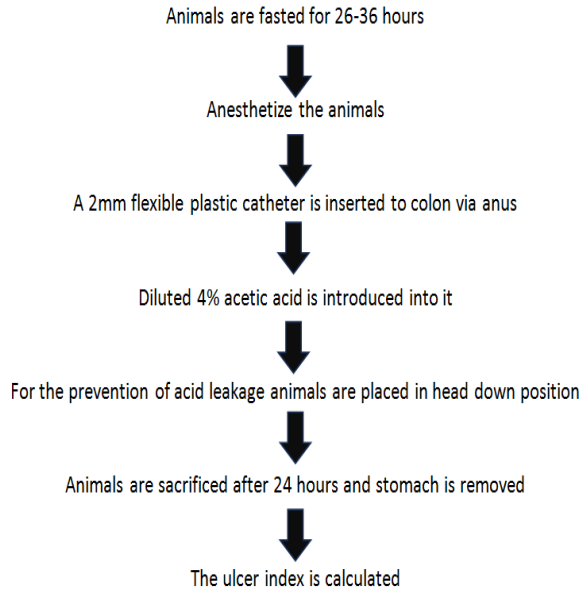


Acidic acid induced gastric ulcer model

Principle: Chronic peptic ulcers can be induced by this method. Potential anti-ulcer activity for chronic ulcers.

- ❖ Animal used: Albino rats
- ❖ Drugs used: Diluted acetic acid (4%)
- ❖ Route of administration: Intra rectal

Procedure

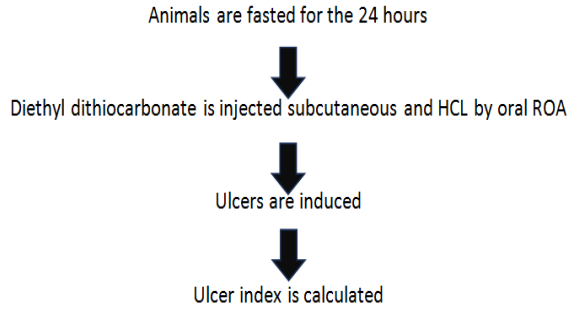


Diethyl dithiocarbonate gastric ulcer induced model

Principle: The free radicles like super-oxide & hydroxyl radicles which plays a major role in the development of ulcers.

- ❖ Gastric ulcer inducing chemical: Diethyl dithiocarbonate with saline, HCL (0.1N)
- ❖ Route of administration: Subcutaneous: Diethyl dithiocarbonate with saline

Procedure

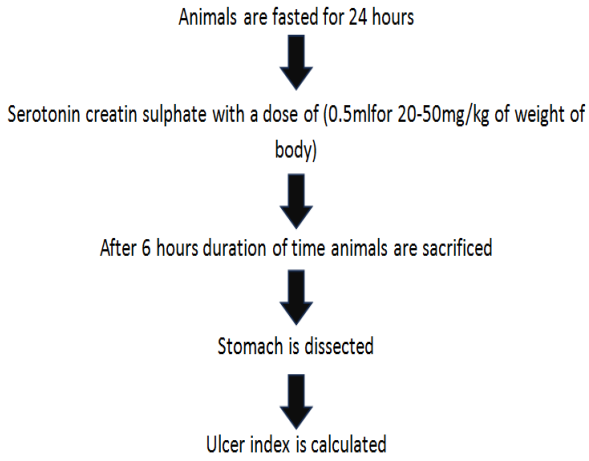


Serotonin gastric ulcer induced model

Principle: The low gastric mucosal flow which may lead to formation of ulcers. Serotonin which is a class of vasoconstriction so the gastric mucosal flow reduced lead to formation of ulcers.

- ❖ Drugs used: Serotonin creatin sulfate
- ❖ Route of administration: Subcutaneous

Procedure



NSAIDs gastric ulcer induced model

Principle: The principle which involved in it is Prostaglandins which help in reducing the ulcers are inhibited by the NSAIDs. NSAIDs are the second most drugs to cause ulcers.

- ❖ Inducing chemicals/drugs:

Aspirin; 150mg/kg
Indomethacin; 40-100mg/kg

- ❖ Route of administration: Oral

Procedure

Animals are fasted 24-36 hours

↓

NSAIDs are adminstered by oral route

↓

Test drug is administered

↓

Animals are dissected after 4 hours

↓

Ulcer index is calculated

Water immersion stress or cold resistance induced ulcer model

Principle: The model which works on the principle of water immersion stress or cold resistance. Histamine which lead to the ulcer formation. It also reduce the mucus production by cells, low blood flow and pancreas juice into bile duct these factors lead to formation of ulcers.

- ❖ Animals used: Mice or rat
- ❖ Drugs used: Test drug

Procedure

Time period of 24-36 hours animals are fasted

↓

Animals will be subjected to water immersion stress

↓

Reference drug is induced to the animals

↓

Animals are placed in individual compartments

↓

Ulcers induce will be observed

↓

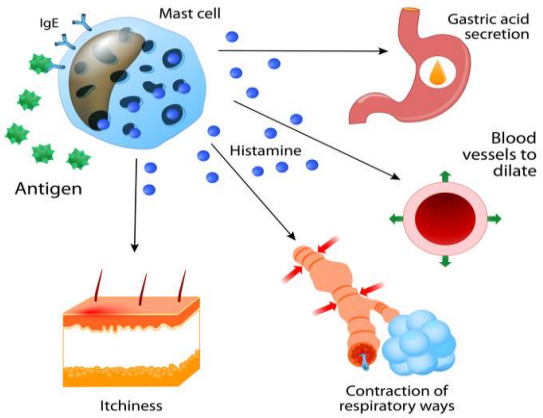
Animals are to be sacrificed& dissected and measure ulcer severity

In case of water immersion induced model the animals are placed in temperature of 15-20 degree Celsius and in case of cold immersion model animals in 2-3 degree Celsius upto the level of the xyphoid levels.

Histamine induced gastric ulcer model

Principle: Mast cells releases histamine - histamine binds with parietal cells – Activates adenyl cyclase – covert ATP into c-AMP secretion of the HCL from the parietal cells done – formation of ulcers.

- ❖ Animals used: Male guniea pig
- ❖ Gastric ulcer inducing chemical: Histamine sulphate
- ❖ Route of administration: Intraperitonially



Procedure

Animals are fasted overnight

↓

50 mg of histamine sulphate injected by intraperitonially

↓

After 4 hours, animals will be sacrificed and dissected the stomach

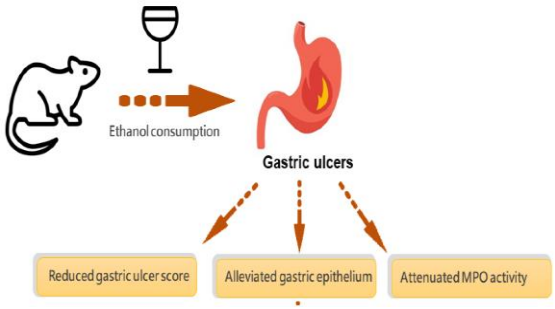
↓

Ulcer index is calculated

Ethanol induced gastric ulcer model

Principle: Ethanol which induces the ulcers by the action releasing of HCL and pepsin on gastric mucosa.

- ❖ Animals used: Wister rats
- ❖ Gastric ulcer inducing chemical: Ethanol
- ❖ Route of administration: Oral



Procedure

Animals fasted last 18 hours before experiment

↓

Test drug administered

↓

Ethanol administered with a dose of 1 ml orally

↓

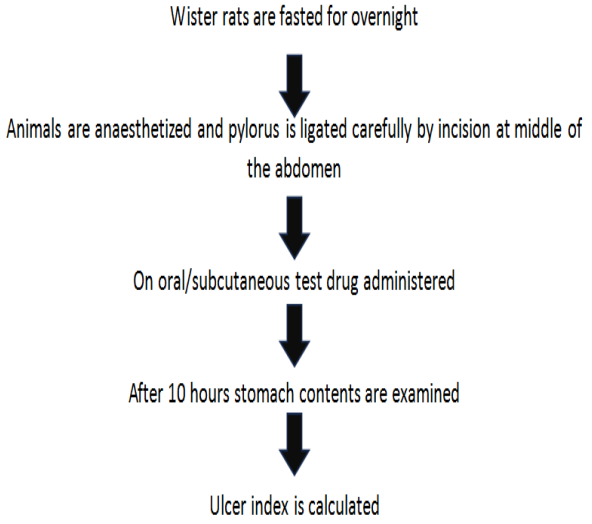
Animals stomach washed with the warm water & ulcer severity observed

Pylorus ligated induced gastric ulcer model

Principle: The Pylorus which connects the duodenum and stomach on which ligated lead to the more accumulation of the gastric acids that is the cause of the ulcer induce.

- ❖ Animals used: Wister rat
- ❖ Surgical method: Pylorus ligation

Procedure



Cysteamine induced duodenal ulcer model

Principle: Duodenal ulcers are 2 types namely acute and chronic. The main causes of this is stimulation of gastric acid secretion and alkaline mucosa inhibition.

- ❖ Animals used: Rats
- ❖ Ulcer inducing chemical: Cysteamine HCL

Cytamine HCL injected 400 mg/kg it produce the acute ulcers and chronic ulcers are induced twice within 4 hours.

Ulcer evaluation parameters & methods used to calculate ulcer severity

The ulcer severity can be calculated by these three methods as follows;

- ✓ Give the score on ulcer severity.
- ✓ Ulcer index (UI) on ulcer score.
- ✓ Percentage of protection ratio & percentage of curative ratio with help of ulcer index.

Give score based on ulcer severity

Score	Ulcer severity
0	No lesions are observed
1	Mucosa was ruptured
2	1-5 small sized lesions (1-2 mm)
3	>5 are intermediate (3-4 mm)
4	≥ 2 intermediate lesions or 1 gross (> 4 mm) lesions
5	Perforated lesions are observed

Ulcer index (UI) based on ulcer score

It follows the formula;

$$\text{Ulcer index (UI)} = \frac{\text{Ulcer score}}{\text{Total number of animals ulcerated}}$$

Percentage of protection ratio & percentage of curative ratio with help of ulcer index

Percentage protection rate:

$$\text{Formula;} \quad \frac{\text{UI of ulcer group}}{\text{UI of ulcer treated grope}} - \frac{\text{UI pre treated drug groups}}{\text{UI of ulcer group}}$$

Percentage curvature ratio:

$$\text{Formula;} \quad \frac{\text{UI of the ulcer group}}{\text{UI of ulcer the treated grope}} - \frac{\text{UI of the treated drug groups}}{\text{UI of the ulcer group}}$$

CONCLUSION

Ulcers are the severe gastrointestinal disease that will leads to severe affects. The in vivo techniques can evaluate the quality and efficacy on anti-ulcer drugs. These preclinical animal model for gastric ulcer and its evaluation techniques will help in the research of anti-ulcer activity.

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