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Titration of Indomethacin Doses Required for Induction of Pepticulceration: A Pilot Study

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Abstract

Background and Objectives: Peptic ulcers are increasingly reported as a challenging disease in clinical settings. The exact pathology is obscure and probably multifactorial, including acidity, infection, erosion, stress, and poly pharmacy. Hence, curably treatment is lacking. The present study aimed to assess the dose of indomethacin that can induce ulcer.

Methods: Thirty albino Wistar rats were used for the pilot study, they were subdivided into three groups, each group contain 10 rats, all were indomethacin treated groups of different doses (low dose indomethacin 25 mg/kg, moderate dose indomethacin 30 mg/kg, and high dose indomethacin 35 mg/kg) and according to microscopic examination; 30 mg/kg of indomethacin was used to induce gastric ulcer for the main study. Stomachs were excised from the rats bodies, and examined macroscopically. Then the stomach tissues were processed for histological examination.

Results: A dose of 30mg indomethacin has successfully induced gastric ulcer.

Conclusion: Titration of the dose give indication about the therapeutic dose of indomethacin which could induce no ulcer in stomach.

Keywords: Peptic Ulcer; Indomethacin; Titration of Dose; Gastric Toxicity

Abbreviation:

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Introduction

Peptic ulcers are acid-induced erosions in the duodenum and stomach [1]. These entities are characterized by the destruction of the mucosa, with the damage extending to the muscular propria or submucosa. Erosions are defined as lesions that do not penetrate the muscular propria [1]. Gastric ulcer is a precise word used to describe an ulcer that particularly occurs in the stomach. Gastric ulcers predominantly occur in the vicinity of the lesser curvature of the stomach, although they can also arise in any location between the pylorus and the cardia [2]. Ulcers in the gastrointestinal (GI) tract can be caused by multiple factors, including Helicobacter pylori infection and smoking [3,4] and/or non-steroidal anti-inflammatory drugs (NSAIDs) include pain relievers like aspirin and indomethacin [5-7].

Indomethacin (INDO), similar to other NSAIDs, works by inhibiting the synthesis of prostaglandins, resulting in both therapeutic advantages and possible adverse effects [8]. Administration of Prostaglandin E2 (PGE2) protects against indomethacin-induced gastrointestinal ulcers through

mechanisms such as enhancing mucus synthesis and thickness, boosting bicarbonate secretion, improving blood supply to the mucosa, and reducing indomethacin-induced hypermotility of the stomach [9]. Furthermore, scientific studies have confirmed that indomethacin effectively reduces the production of gastrointestinal mucus and increases the likelihood of developing ulcers [10].

Materials And Methods

This study conducted at the University of Mosul in Iraq, which was approved by the Institutional Animal Welfare Committee and the Graduate Studies Committee. The study was conducted over a period of 10/9/2023 to 10/1/2024 at the animal house of the College of Veterinary Medicine, with support from the Department of Pharmacy and Toxicology. Thirty Albino Wistar rats were used, housed in metallic cages with specific environmental conditions and acclimated for one month before the start of the experiment. Indomethacin, a medication containing 25 mg of indomethacin, was administered to the rats in a specific dose. The rats were euthanized according to the standards of the American Veterinary Medical Association, and their stomachs were examined for pathological processes. Histological slides were prepared for analysis.

Tissue Processing Includes the following Steps:

This process of tissue collection and fixation, which is necessary to preserve tissues and prevent decomposition. The choice of fixatives depends on the tissue type and desired qualities. The goal is to maintain the tissues in their natural state and prevent self-decomposition and bacterial infection. The process involves extracting the tissue, washing and separating it from surrounding tissue, and then immersing it in a solution. The text also mentions the importance of careful handling to avoid any impact on examination.

The process of securing rat stomachs to a corkboard, inscribing identifying information, and checking for ulcers. The stomachs were then photographed and stored in a solution of neutral buffered formalin for 48 hours before further processing.

The process of tissue processing and preparation for microscopic examination. This includes steps such as washing, dehydration, clearing, impregnation, embedding, trimming, sectioning, and staining. The tissues are first washed to remove the fixative, then dehydrated using alcohol, and cleared using a solvent. The tissues are then impregnated with paraffin wax, embedded in a block, and trimmed for optimal cutting. The microtome is used to cut thin slices of the tissue, which are then stained using hematoxylin and eosin. After staining, the tissues are deparaffinized and processed for microscopic examination. This involves a series of ethanol washes, cleaning with xylene, and impregnation with paraffin wax. The tissues are then ready for microscopic examination.

Results

G1: Control group: A light microscopic examination of the gastric tissue shows normal gastric mucosa, submucosa, and muscularis.
G2: Indomethacin 25 mg/ kg group: A light microscopic examination of the gastric tissue at (100X) shows signs of mild to moderate hemorrhage in gastric mucosa, mild vacuolar degeneration of gastric glands cells, infiltration of inflammatory cells and congestion of blood vessels in submucosa.
G3: Indomethacin 30 mg/ kg: A light microscopic examination of the gastric tissue at (100X) shows signs sever hemorrhage in the surface of mucosa, vacuolar degeneration of gastric glands cells, infiltration of inflammatory cells and hemorrhage in the deep layer of mucosa.
G4: Indomethacin 35 mg/ kg: A light microscopic examination of the gastric tissue at (100X) shows signs sever hemorrhage in the mucosa, vacuolar degeneration of gastric glands cells, necrosis, infiltration of inflammatory cells, hemorrhage and fibrosis in the deep layer of mucosa.

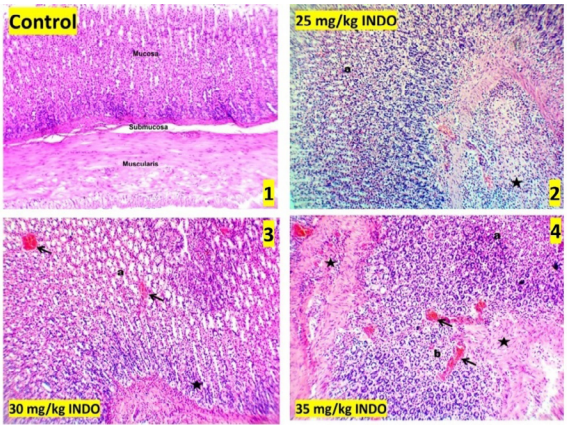

Figure 1: Photomicrographs of gastric tissue.

(1): negative control group, (2): Histological section of rat stomach of 25mg group showing the (arrows) mild to moderate hemorrhage in gastric mucosa, (a) mild vacuolar degeneration of gastric glands cells and (star) infiltration of inflammatory cells and congestion of blood vessels in submucosa. H&E stain 100x. (3): Histological section of rat stomach of 30mg group showing the (arrows) sever hemorrhage in the surface of mucosa, (a) vacuolar degeneration of gastric glands cells and (star) infiltration of inflammatory cells in the deep layer of mucosa. H&E

stain 100x. (4): Histological section of rat stomach of 35mg group showing the (arrows) sever hemorrhage in the mucosa, (a) vacuolar degeneration of gastric glands cells and (b) necrosis (star) infiltration of inflammatory cells, hemorrhage and fibrosis in the deep layer of mucosa. H&E stain (100x).

Discussion

The pilot trial involved the oral administration of indomethacin to rats that have undergone a 24-hour fasting period, to induce stomach ulcers. The selection of indomethacin as the initial medicine for creating an experimental ulcer model was primarily driven by its greater tendency to cause ulcers in comparison to other NSAIDs [3,4,11]. The administered doses of indomethacin were 25mg/kg, 30mg/kg, and 35mg/kg. The larger dosage demonstrated notable toxicity in rats, leading to the death of cells in the stomach glands, extensive bleeding in the mucosal lining, and bleeding and scarring in the inner layer of the mucosa, potentially causing permanent damage. Conversely, the lesser dosage resulted in mild to severe bleeding of the mucous membranes, the presence of inflammatory cells, and increased blood flow in the layer beneath the mucosa, but did not produce the intended ulcers. Thus, the dosage of 30 mg/kg was chosen to induce gastric ulcers. The findings of our investigation are consistent with prior research carried out by Mugo, et al. [1], who also employed a dosage of 30 mg/kg of indomethacin to induce gastric ulcers in Wistar rats [1].

Pilot research has shown that ulceration was caused by a single oral dose of indomethacin (30 mg/kg body weight). The findings align with the study conducted by Sabiu et al. (2015), which revealed that administering 30 mg/kg of indomethacin orally resulted in a notable ($p < 0.05$) rise in the level of ulceration (ulcer index) in rats [12].

Conclusion

Titration of the dose is a critical methodology in determining the optimal therapeutic dose of indomethacin that can mitigate its ulcerogenic effects on the stomach. By carefully titrating the dose—starting with a lower dosage and gradually increasing it while closely monitoring the patient's response and any adverse effects—it is possible to identify a therapeutic window where the efficacy of indomethacin in relieving symptoms is maximized, while minimizing gastrointestinal toxicity. This approach allows clinicians to balance the anti-inflammatory benefits against the potential risks more precisely.

References

1. Mugo NW, Wangia C, Kikuvi G, Ngugi S (2020) Antiulcerogenic effect of Capparis cartillaginea decne on indomethacin-induced gastric ulcer in Wistar rats. International Journal of Research in Medical Sciences 8(10): 3445.

2. Mohammed TA, Al-Zubaidy AA, Ramadhan MA, Khudur RK (2019) The Effects of trimetazidine against ischemia-induced ulcer in rabbit ear model. Pharmacologyonline 1(1): 64-86.

3. Abdullah E, Dhiaa S, Saleh K, Merkhan M (2021) Effect of esomeprazole on lipid profile in patients with peptic ulcer. Pharmacia 68: 613-617.

4. Merkhan MM, Abdullah E, Althanoon Z (2022) Effect of Esomeprazole on serum creatinine and urea in patients with Peptic Ulcer. Research Journal of Pharmacy and Technology 15(1): 160-164.

5. Romano M, Ricci V, Di Popolo A, Sommi P, Blanco CD, et al. (1998) Helicobacter pylori upregulates expression of epidermal growth factor-related peptides but inhibits their proliferative effect in MKN 28 gastric mucosal cells. The Journal of Clinical Investigation 101(8): 1604-1613.

6. Al-Moutairy AR, Tariq M (1996) Effect of vitamin E and selenium on hypothermic restraint stress and chemically-induced ulcers. Digestive diseases and sciences 41: 1165-1171.

7. Abdulqader SW, Faisal IM, Saeed MG, Merkhan MM (2022) Fluvoxamine suppressed oxidative stress associated with tissue erosion. Research Journal of Pharmacy and Technology 15(2): 819-824.

8. Tolman EL, Rosenthale ME, Capetola RJ, Mcguire JL (1984) Suprofen: the pharmacology and clinical efficacy of a new non-narcotic peripheral analgesic. Clinics in Rheumatic Diseases 10(2): 353-368.

9. Kollberg B, Nordemar R, Johansson C (1981) Gastrointestinal protection by low-dose oral prostaglandin E2 in rheumatic diseases. Scandinavian Journal of Gastroenterology 16(8): 1005-1008.

10. Takeuchi K, Tanaka A, Hayashi Y, Yokota A (2005) COX inhibition and NSAID-induced gastric damage-roles in various pathogenic events. Current topics in medicinal chemistry 5(5): 475-486.

11. Tanaka KI, Tomisato W, Hoshino T, Ishihara T, Namba T, et al. (2005) Involvement of intracellular Ca2+ levels in nonsteroidal anti-inflammatory drug-induced apoptosis. Journal of Biological Chemistry 280(35): 31059-31067.

12. Sabiu S, Garuba T, Sunmonu T, Ajani E, Sulyman A, et al. (2015) Indomethacin-induced gastric ulceration in rats: Protective roles of Spondias mombin and Ficus exasperata. Toxicology reports 2: 261-267.