WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 12, 106-114 Research Article ISSN 2278 – 4357

ACETYLSALICYLIC ACID INDUCES DOSE DEPENDENT GASTRIC ARCHITECTURE DISTORTIONS AND GLANDULAR EPITHELIUM ULCERATIONS IN WISTAR RATS

Idehen I. Charles*[1], Bankole J. Kayode[1], Airhomwanbor Kingsley[1], Dic-Ijiewere Ebenezer[2], Okparaku Sunday[1], Ehimara Raphael[2], Osarobo Eseiwi[3] and Oigbochie Princess[1]

[1]Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, College of Medicine, Ambrose Alli University, Ekpoma-Nigeria.

[2]Department of Chemical Pathology, Faculty of Clinical Sciences, College of Medicine, Ambrose Alli University, Ekpoma-Nigeria.

[3]Department of Heamatology, Faculty of Clinical Sciences, College of Medicine, Ambrose Alli University, Ekpoma-Nigeria.

Article Received on
30 September 2018,

Revised on 21 Oct. 2018,
Accepted on 11 Nov. 2018,

DOI: 10.20959/wjpps201812-12698

***Corresponding Author**
Idehen I. Charles
Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, College of Medicine, Ambrose Alli University, Ekpoma-Nigeria.

ABSTRACT

Acetylsalicylic acid- herein commonly refers to as aspirin, is a nonsteroidal anti-inflammatory drug (NSAID) with symptomatic relief of pain, fever and inflammation for which reason it is widely used. The aim of the study is to investigate the effect of vary aspirin dose on the histological architecture of the stomach using Wistar rats as a model. The experiment was conducted on 30 adult male Wistar rats (weighing between 160 to 200g) divided into 5 groups; a control (group A) and 4 test groups (groups B, C, D and E) treated daily with 35, 70, 105 and 140 mg/kg per body weight of aspirin respectively for 4 weeks. At the end of treatments, rats were anesthetized and following cervical decapitation, the stomach was dissected out for gross and histological examination. There were dose dependent distortions of gastric histological architecture, glandular epithelium ulceration and haemorrhage in groups treated with 105mg/kg and 140mg/kg doses of aspirin as compared to normal histological architecture seen in groups treated with 70mg/kg and 35mg/kg doses and with the control. Based on the findings, aspirin may have no effect on the stomach at low dosage but causes haemorrhagic ulcerations and alteration in gastric histology at higher doses.

KEYWORD: Aspirin, Non-steroidal anti-inflammatory drug, Gastrointestinal, Gastric ulceration.

INTRODUCTION

Acetylsalicylic acid (Acetylated salicylate) commonly known as aspirin, is classified among the nonsteroidal anti-inflammatory drugs (NSAIDs).[1] These agents reduce the signs and symptoms of inflammation and exhibit a broad range of pharmacological activities, including analgesic, antipyretic, and antiplatelet potentials. Aspirin was first introduced by the drug and dye firm Bayer in 1899. Aspirin and the other NSAIDs do not generally change the course of the disease process in conditions where they are used, the action is mainly for symptomatic relief such as to relieve pain, inflammation and fever and prevent clot formation.[2] Aspirin in its present form has been around for over 100 years and is still one of the most widely used medications in the world with an estimated approximately 40,000 metric tons of it is consumed annually.[3] It remains a common analgesic and a widely prescribed antiplatelet therapy for cardiovascular and cerebrovascular disease, and thus aspirin toxicity remains an important clinical problem.[1]

Aspirin as well as other NSAIDs are often used as analgesic to relieve minor aches and pains, antipyretic to reduce fever and as anti-inflammatory medication.[4] It also has antiplatelet or anti-clotting action and used in long-term, low doses to prevent heart attacks, strokes and blood clot formation in at risk for developing blood clots patients. Higgs *et al.*[5] established that low doses of aspirin can be given immediately after a heart attack to reduce the risk of another heart attack or cardiac tissue death. Paterson *et al.*[6] recommended aspirin for the prevention of major adverse cardiovascular events like composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death in diabetic patients without previous cardiovascular disease

It is also well known that, aspirin is rapidly absorbed from the stomach and small intestine, primarily by passive diffusion across the gastrointestinal (GI) tract which is rapidly hydrolyzed to salicylic acid by esterase in the GI mucosa and blood plasma. It dispersed throughout the body after ingestion, with the highest concentrations found in the blood plasma, liver, renal cortex, heart and lungs.[7] Normally the stomach has three defenses against digestive juices: mucus that coats the stomach lining and shields it from stomach acid, the chemical bicarbonate that neutralizes stomach acid, and blood circulation to the stomach lining that aids in cell renewal and repair.[8] NSAIDs hinder all of these protective

mechanisms and cause damage to the sensitive stomach lining to result in ulcers.[5] Aspirin often causes acute gastric mucosal damage that can be seen endoscopically or assessed indirectly (by measuring gastrointestinal blood loss) with the occurrence of most adverse effects apparently related to the dose administered.[9] The occurrence of gastric adaptation, or lessening injury with continued treatment, obscures the interpretation of results from studies of acute administration and evidence of dose-response effects has frequently been ignored when. The absence of symptoms does not correlate with acute or chronic mucosal damage and appears to have no predictive value.[10] Endoscopic studies linking the extent and degree of acute mucosal injury to various nonsteroidal anti-inflammatory drugs have little or no value in predicting the frequency or severity of chronic gastric ulcer or gastrointestinal bleeding. Therefore, this study was conducted to evaluate the effect of varying dose treatments of aspirin on the histology of the stomach considering that the stomach serves as it first point of contact.

MATERIALS AND METHODS

Aspirin (containing 300 mg/tablet acetylsalicylic acid) with trade name Emzor pharmaceutical was purchased from a pharmacy in the study area. This experimental study was conducted in the histological laboratory of Ambrose Alli University, Ekpoma- Nigeria. A total of 30 adult male Wistar rats weighing between 160 - 200g were procured from the Animal Farm, College of Medicine, Ambrose Alli University, Ekpoma and transferred to the site of experiment where they were allowed 2 weeks of acclimatization. They were kept in wire mesh cages with tripod that separates the animal from its faeces to prevent contamination. During the period of acclimatization, the rats were maintained in accordance with the standard guide for the care and use of Laboratory animals and fed rat chow and clean water *ad libitum*.

The Wistar rats were divided into 5 groups. Group A served as the control and groups B, C, D and E rats were treated daily with 35mg/kg, 70mg/kg, 105mg/kg and 140mg/kg body weight respectively. The aspirin solution was prepared daily by grinding the aspirin tablets and diluting the powder in clean measured quantity of water. Using 1ml syringe, the corresponding dose per body weight was given by gavage to each rat. The treatment was carried out daily for four weeks.

At the end of treatment, each rat was cervically decapitated after anesthetized and the stomach harvested, cleaned with phosphate buffer and dried with blotting paper before gross

observation. Thereafter, the stomachs were fixed in 20% Formalin in labeled sample bottles for histological processing. The classical paraffin sectioning (3-5µ thick) was cut, stained with haematoxylin and Eosin staining technique and observed under light microscopy for histopathological examinations as previously documented in Idehen et al.[11] and micrographic pictures taken.

RESULT

Figure 1 presented the mean body at baseline, termination of experiment and weight gain of rats treated on varying doses of aspirin for 4 weeks. Except for the group treated with 35mg/kg aspirin, there was body weight lost in aspirin treated groups compared to the control. Gross evaluations of the stomachs showed comparable gastric mucosal in the control, 35mg/kg and 70mg/kg aspirin treated groups but mucosal inflammations and ulcerations in the 105mg/kg and 140mg/kg aspirin treated groups (*Table* 1).

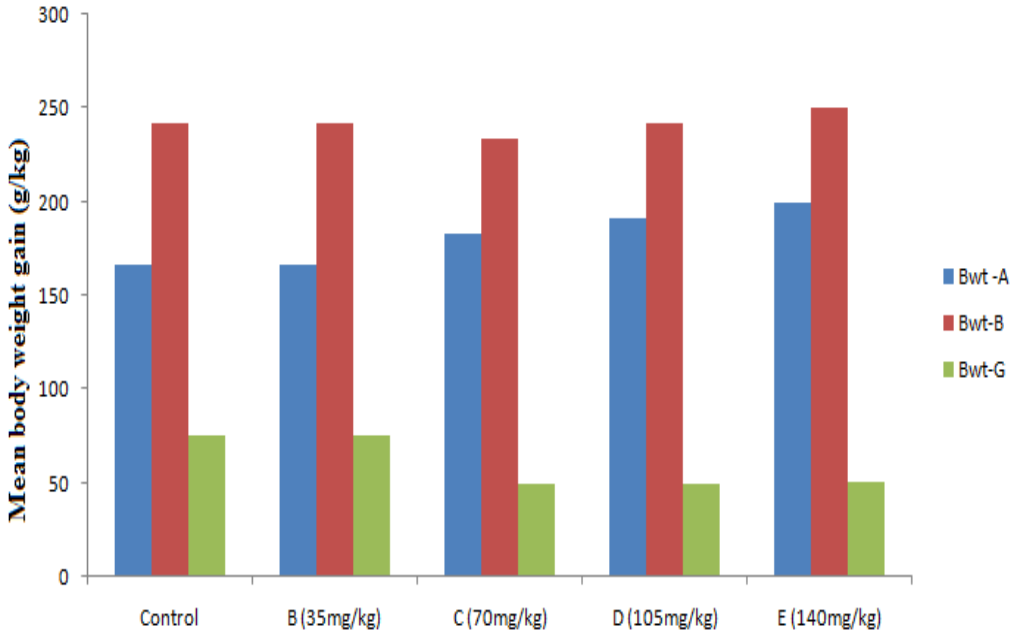

Figure 1: Mean body weight gain after varying dose aspirin treatment for 30 days.

Key: Bwt-A = weight before experiment, Bwt-B = weight after experiment, Bwt-G = body weight gain; values are mean ± standard deviation.

Table 1: Gross and histological observations in the stomach of Wister rats treated with vary doses of aspirin.

Group	Dose of Aspirin (mg/kg bwt)	Gross findings	Microscopic observations
A	Nil	Normal (6/6)	Nil
B	35	Normal (6/6)	Nil
C	70	Normal (4/6) mucosal inflammations (2/6)	Nil
D	105	mucosal inflammations (6/6), ulcerations (5/6)	Distorted histology (6/6), ulceration (6/6) and hemorrhage (6/6)
E	140	mucosal inflammations (6/6), ulcerations (6/6)	Distorted histology (6/6), ulceration (6/6) and hemorrhage (6/6)

Note: numbers in bracket signifies the number of rats affected over the total number of rats in the group.

Microscopic examinations showed normal histology sections of the serosa (S), muscular layer (M), submucosa (B), gastric glands (G) and peptic/chief cells (C) clustered at the base of the glands in the control (Group A). Similar histological findings were observed in groups treated with 35mg/kg (group B) and 70mg/kg (group C) aspirin. However, there were dose depended distorted gastric histological architecture, ulceration of the glandular epithelium (R) and haemorrhage (H) in groups treated on 105mg/kg (group D) and 140mg/kg (group E) aspirin (see *plate* 1).

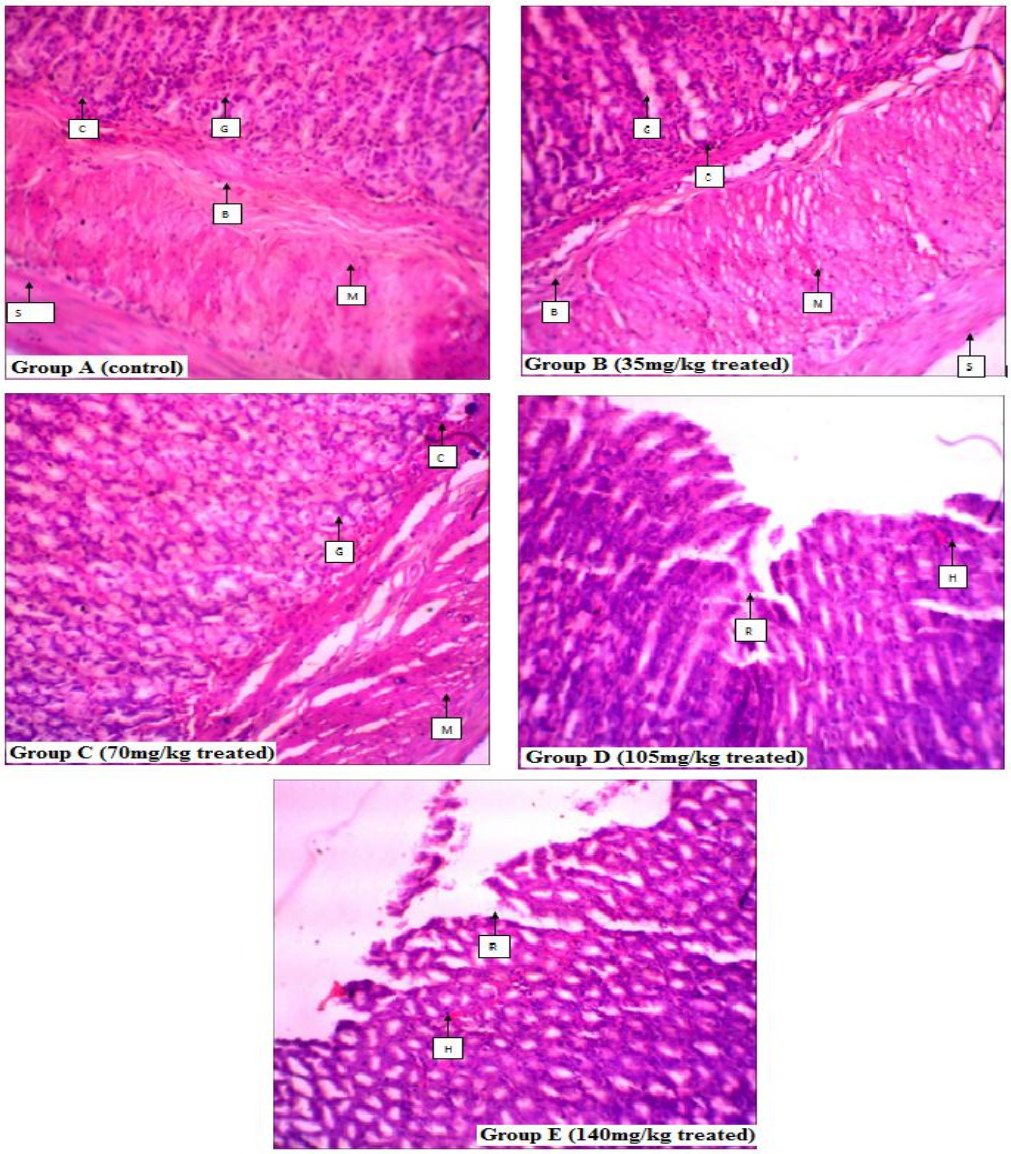

Plate 1: Histological presentations of the stomach of rats treated with varying doses of aspirin compared to control (H&E x 100).

DISCUSSION

The results of this study showed comparable body weight gain in rats treated on 35mg/kg of aspirin with the control but non-significant lower body weight gain in groups treated on 70mg/kg to 140mg/kg aspirin. Done *et al.*[12] has reported similar findings and concluded that aspirin does not affect the metabolism of carbohydrate pathway.

Microscopic examinations showed similar gastric architectures in rats treated on 35mg/kg and 70mg/kg of aspirin with the control but altered gastric histology in groups treated on 70mg/kg to 140mg/kg aspirin. The observed comparable gastric architectures in rats treated on 35mg/kg and 70mg/kg of aspirin with the control corroborate with the findings by with

Ensign *et al.*,[13] who concluded that the doses of 35mg/kg and 70mg/kg are not adequate to produce complete therapeutic effect. However, Forsyth et al.[14] has reported gastric lesions ranging from mild petechiation to linear hemorrhage in dogs receiving 35 mg/kg of plain aspirin. The difference in this study and that by Forsyth et al.[14] maybe due to the animal difference which might indicates that different animals react differently to aspirin. Also, the difference in age and size of the animals may have contributed to the different findings.

In the present study however, aspirin at doses of 105mg/kg and 140mg/kg was observed to cause distortion of gastric histological architecture, glandular epithelium ulceration and haemorrhage in a dose dependent fashion. These findings are in agreement with the findings by Iwamoto *et al.*[15] who documented aspirin at these doses to be used for the induction of gastric ulcers. It was concluded by Iwamoto *et al.*[15] that these finding confirmed the reported incidence of upper gastrointestinal damage in patients taking long-term aspirin. Also, according to Xiao *et al.*[16], interaction process between NSAID and stress may cause lesion of stomach mucosa. The mechanism of action of NSAIDs induced gastrointestinal damage can be divided into local and systemic actions. According to La Casa *et al*.[17], aspirin is a more potent inhibitor of cyclooxygenase-1 (COX-1) than (COX-2). The pathogenesis related to inhibition of COX-1 includes reduction in mucosal flow, mucus and bicarbonate secretions, and impaired platelet aggregation while inhibition of COX-2 causes reduction of angiogenesis and increase of leukocyte adherence. The pathogenesis related to direct epithelial damage involves acid back diffusion and impaired platelet aggregation. Aspirin often causes acute gastric mucosal damage that can be seen endoscopically or assessed indirectly (for example, by measuring increased gastrointestinal blood loss). The occurrence of most adverse effects is apparently related to the dose administered. This dose-response effect, evident in both endoscopic and microbleeding studies done after acute or short-term aspirin administration, is also associated with the risk of developing chronic gastric ulcer.[18]

Judging by the findings of this study, aspirin at low dosage may have no effect on the stomach histology, however, it causes a dosage dependent distortion of the gastric architecture, glandular epithelium ulceration and haemorrhage at a higher dosage and longer duration of ingestion. It is therefore recommended that aspirin be administrated strictly on prescription and further studies be carried out on the effect of aspirin on the stomach in other animal models.

REFERENCES

1. Silverstein F.E., Faich G., Goldstein J.L. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study, 2000; 284: 1247.
2. Pillinger M.H., Capodici C., Rosenthal P. Modes of action of aspirin-like drugs: salicylates inhibit erk activation and integrin-dependent neutrophil adhesion. *Proceedings of the National Academy of Sciences, U S A., 1998;* 95: 14540.
3. Picot D., Loll P., Garavito R. The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. *Nature, 1994;* 367: 243-249.
4. Vane J. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature, 1971*; 231: 232-235.
5. Higgs G.A., Salmon J.A., Henderson B., Vane J.R. Pharmacokinetics of Aspirin and Salicylate in Relation to Inhibition of Arachidonate Cyclooxygenase and ntiinflammatory Activity. *Proc. Natl. Acad. Sci. USA, 1987;* 84: 1417-1420.
6. Paterson J.R., Baxter G., Dreyer J.S., Halket J.M., Flynn R., Lawrence J.R. Salicylic Acid sans Aspirin in Animals and Man: Persistence in Fasting and Biosynthesis from Benzoic Acid. *Journal of Agriculture and Food Chemistry, 2008;* 56: 11648-11652.
7. Marcia L.B. Use of Aspirin in Children with Cardiac Disease. *Pediatric Pharmacotherapy,* 2007; 13(2).
8. Hoffmann F. Acetyl Salicylic Acid. U.S. Patent, 644,077. 1900.
9. Amin A.R., Vyas P., Attur M. The mode of action of aspirin-like drugs: effect on inducible nitric oxide synthase. *Proceedings of the National Academy Sciences U S A., 1995;* 92: 7926.
10. Kopp E., Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science, 1994;* 265: 956.
11. Idehen I. Charles, Bankole J. Kayode, Airhomwanbor Kingsley, DIC-Ijiewere O. Ebenezer, Eidangbe A. Peace. Spleen Histological Changes Following Monosodium Glutamate Ingestion in Adult Male Wistar Rat. *Advances in Biomedical Sciences, 2017;* 2(1): 1-5.
12. Done J.D., Rudick C.N., Quick M.L., Schaeffer A.J., Thumbikat P. Role of mast cells in male chronic pelvic pain. *Journal of Urology, 2012;* 187(4): 1473-1482.

13. Ensign L.M., Cone R., Hanes J. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. *Advances of Drug Delivery Reviews, 2012;* 64(6): 557-570.
14. Forsyth S., Guilford W., Haslett S. Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. *Journal of Small Animals Practice, 1998;* 39: 421-424.
15. Iwamoto J., Saito Y., Honda A., Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term aspirin therapy. *World Journal Gastroenterol, 2013;* 19(11): 1673-1682.
16. Xiao X., Zhao Y., Yuan H., Xia W., Zhao J., Wang X. Study on the effect of rhizoma Curcuma longa on gastrin receptor. *Zhong Yao Cai, 2002;* 25(3): 184-185.
17. La Casa C., Villegas I., Alarcón de la Lastra C., Motilva V., Martín Calero M.J. Evidence for protective and antioxidant properties of rutin, a natural flavone, against ethanol induced gastric lesions. *J Ethnopharmacol, 2000;* 71: 45-53.
18. Dreser H. Pharmacological One on Aspirin (Acetylsalicylic Acid). *Pflugers Archives, 1899;* 76: 306-318.