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ORIGINAL ARTICLE

The Effect of Ibuprofen, Ponstan and Panadol Oral Suspensions on the Gastrointestinal Mucosal Layer in Mice

Seeham Ali Alkafajy*, Abeer Salih Ali

Lecturers, Biology Department, Science College, Mustansiriyah University, Baghdad, Iraq

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KEYWORDS

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ABSTRACT: Antipyretic drugs such as suspensions of Mefenamic acid (Ponstan), Ibuprofen and paracetamol (acetaminophen) are the most common drugs that wildly used in children to decrease the fever, pain and inflammation, and from clinical observations of children using these drugs, found they cause gastrointestinal complications and from this, the idea of this research was to find the effect of these drugs on the mucous membrane of the gastrointestinal tract in Swiss albino mice.In the present study, we used 30 mice classified into five groups which are G1 as control group, G2 receive 15 mg kg $^{-1}$day^{-1} panadol, G3 receive 30 mg kg^{-1}day^{-1}ibuprofen, G4 receive 5 mg kg^{-1} day^{-1} Ponestan and G5 receive a combination of panadol and ibuprofen in same the previously doses respectively for 7 days. The gastric histological sections of G2 were normal mucosal, G4 shown mild mucosal glandular hyperplasia, while G3 and G5 groups appear flat mucosal surface with submucosal hyperplasia of gland mild atypical cells, and G2 showing mucosal glandular hyperplasia. The intestine histological sections of G2 appears normal intestinal villi with mild inflammatory cells infiltration, G3 shown dispersed slight shortening of intestinal villi with mild inflammatory cells infiltration, finally G4 and G5 shown villi hyperplasia with a slight widening of villi with mild inflammatory cells infiltration. NSAIDs are available over-the-counter drugs for adult and in pediatric population And it is considered a safe medicine if used in properly dose in the short-term, the decision to pick an antipyretic should be dictated by safety, efficacy, effectiveness, duration of action and the integrity of the patient gut.

INTRODUCTION

Fever is one of the important and common symptoms in pediatric diseases[1] and known as a combination physiologic response to a disease, occur due to mediated by pyrogenic cytokines and characterized by increased in an essence temperature, generation of acute phase reactants and activation of immune systems[2] .Children are more susceptible to fever, may be associated with increased morbidity, such as seizures, brain damage or death , [3] doctors usually prefer to describe antipyretics, drug agents, for the feverish child to decrease the temperature and parents anxiet. [4] Around the world, the most common drugs used for fever, pain and inflammation are non-steroidal anti-inflammatory (NSAIDs) agents, as Mefenamic acid (Ponstan) and Ibuprofen[5],they have both anti-inflammatory and analgesic properties[6] while paracetamol (acetaminophen) is an analgesic and

*Corresponding author: seehamalkafajy@uomustansiriyah.edu.iq (S. A. Alkafajy)
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antipyretic medication and it not classified as a member of the non-steroidal anti-inflammatory drugs (NSAIDs) [7] , wildly used in children because of its high effectiveness and good safety profile [8] .

Mefenamic acid (Ponstan) is a strong inhibitor of Cyclooxygenase, and has an analgesic action. This drug commonly used in patients was suffering from arthritis, injuries, rheumatoid, osteoarthritis and dysmenorrhea [9].

Ibuprofen is a non-selective inhibitor of cyclooxygenase-1(COX-1) and Cyclooxygenase-2 (COX-2) [10]. In spite of its anti-inflammatory properties may be weaker than some other NSAIDs, it has a prominent antipyretic and analgesic role [11].

paracetamol absorbed in the gastrointestinal tract and reach to peak in plasma concentration about 30 minutes and approximately time that need to maximal temperature reduction is 2 hours[12], although mechanism action of this drug is not completely understood, it is supposed that the acetaminophen-caused antipyretic occurs by central inhibition of the enzyme Cyclo¬oxygenase (COX), although its beneficial effects, poisoning, kidney failure and hepatotoxicity are the gravest adverse effects of Paracetamol, which may happen due to acute exposure[13,14]. It has been reported that the combined use of Paracetamol and ibuprofen reduce fever very rapidly for the first three hours after the second dose, compared with either Paracetamol or ibuprofen give it alone, while another study explained this combination of these tow drugs uncertain that it is more effective to improve the comfort in febrile children compared to a single antipyretic agent (monotherapy) [15].

It is necessary to determine the reason of fever and then provide effective treatment to give the body a chance to respond against the pathogen that causes the fever, and the decision to pick an antipyretic should be dictated by safety, efficacy, effectiveness, duration of action, and cost [16].

The aim of the present study was to demonstrate the effects of frequency administration of some pyrogenic reducer on the structure of the gastrointestinal mucosa in the healthy adult mice.

MATERIALS AND METHODS

Experimental animals

Thirty (30) adult male albino mice were used in this study. The mice brought from the animal house of Baghdad medical college most mice weight about 18–20 g, were selected for the study. Experience was from 15th to 22st February 2020.The animals separated into five groups each group consists of six animals maintained in animal house of Mustansiriyah University /sciences College, The animals were housed in polypropylene cages under hygienic conditions and maintained at normal room temperature (20-22°C), the animals were allowed food and water ad libitum and led the animals adapted in this condition for 7 days Until the experiment start, the groups as the following:

Group 1: control group without any treatment,

Group 2: were given 15 mg kg^{-1}day^{-1} divided into 4 doses as 0.01 mg dose^{-1} of panadol suspension orally using a stomach cannula every 6 houre for 7 dayes,

Group3: were given 30 mg kg^{-1}day^{-1} divided into 4 doses as 0.0075 mg/dose ibuprofen suspension orally using a stomach cannula every 6 hours for 7 days

Group 4: were given 5 mg kg^{-1}day^{-1} divided into 4 doses as 0.005 mg/dose. Of ponstan (mefenamic acid) suspension orally using a stomach cannula every 6 hours for 7days

Group 5: were given mix of (15 mg kg day^{-1} divided into 4 doses as 0.01 mg dose^{-1}) and (30 mg kg day^{-1} divided into 4 doses as 0.0075 mg dose^{-1}) of Panadol and ibuProfen suspension respectively via oral rout every 6 hours for 7 days.

Experimental technique

The drugs used including [panadol syrup 120 mg / 5 ml (GlaxoSmithKline group companies Farmaclair, Herouvile France) at 15 mg/kg/day ibuprofen syrup 100 mg 5 ml^{-1}], [(medfarma U.A.E) at 30 mg kg^{-1} day^{-1}] and [Mefenamic acid –Ponstan- syrup 50 mg / 5 ml (Mission Vivacre

limited – India) at 5 mg $kg^{-1}day^{-1}$] .The animals were observed in their cages for clinical symptoms daily. At the end of the experimental period.

Preparation of histopathological slides

The animals were anesthetized using chloroform and then dissected; the organs such as the stomach, and small intestine were isolated into 10% saline formalin and then subjected to histological procedures and preparation of tissue slides as directed by Banchroft et al [17].

RESULTS AND DISCUSSION

The study revealed differences effects of pediatric antipyretic syrup that use in this study on gastric and intestine mucousal layer , The stomach histological sections of a group (2) treated with 0.01 mg $dose^{-1}$ of panadol suspension showing look- like normal mucosal (Figure1 B) compared with the control in group 1 (Figure1A), group (3) that treated with 0.0075 mg/dose ibuprofen suspension showing flat mucosal surface with sub mucosal hyperplasia of gland mild atypical cells (Figure1 C) compared with control that doesn't appear any change in same layer and cell, group (4) treated with 0.005 mg/dose. Of ponstan (mefenamic acid) suspension, showing look- like normal mucosal but with mild mucosal glandular hyperplasia (Figure1D), group (5) Receive mix of (0.01 mg $dose^{-1}$ and 0.0075 mg $dose^{-1}$) of panadol and ibuprofen respectively showing mucosal glandular hyperplasia (Figure1E).

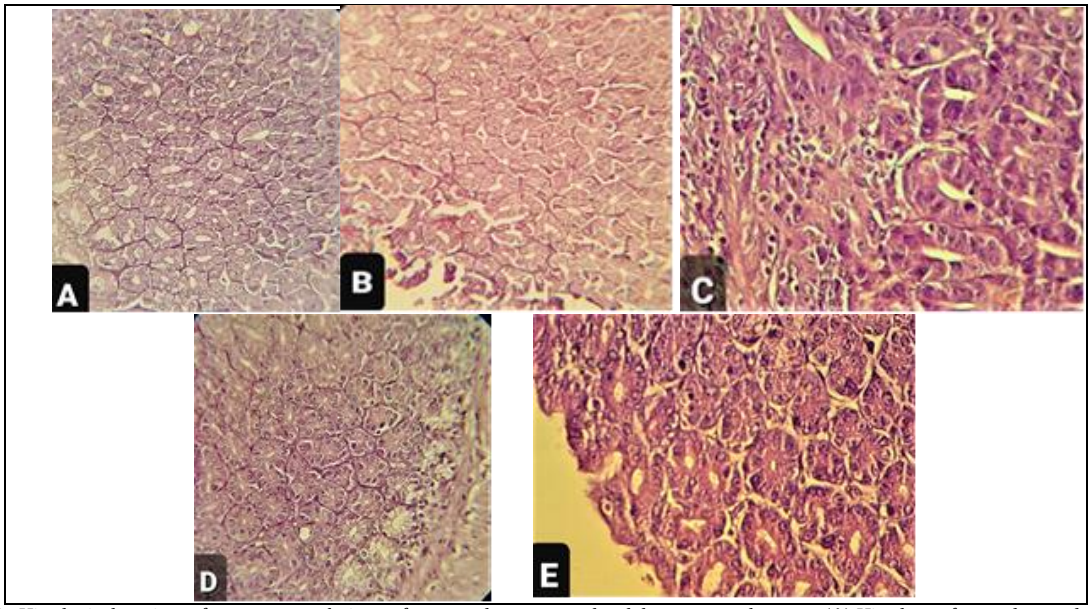

Figure 1. Histological sections of mouce stomach tissues from non demoncetreted and demoncetreted groups. (A) Histology of normal control mouce stomach (X40) ; (B) showing look- like normal mucosal - histopathological changes seen in mouce treated with panadol , (C) Section from mouce treated with ibuprofen showing flat mucosal surface with submucosal hyperplasia of gland mild atypical cells , (D) section look- like normal mucosal but with mild mucosal glandular hyperplasia ,treated with ponstan , (E) showing mucosal glandular hyperplasia section from mouce treated wih mix(panadol and ibuoprofen).

As for the histological sections of the mouce intestine treated with all doses that mentioned previously showed the following; group (2) that treated with panadol look-like normal appearance of intestinal villi with mild inflammatory cells infiltration (Figure 2 B) compared with control group (Figure2 A),while group 3 with ibuprofen look-like normal appearance of intestinal villi with mild inflammatory cells infiltration (Figure 2 C), group (4) with ponstan treatment, showing widening of intestinal villi with inflammatory cells infiltration inside the villi (Figure 2 D) , group (5) treated with mix (panadol and ibuprofen)**,** showing intestinal villi hyperplasia with slight widening of villi (Figure2 E).

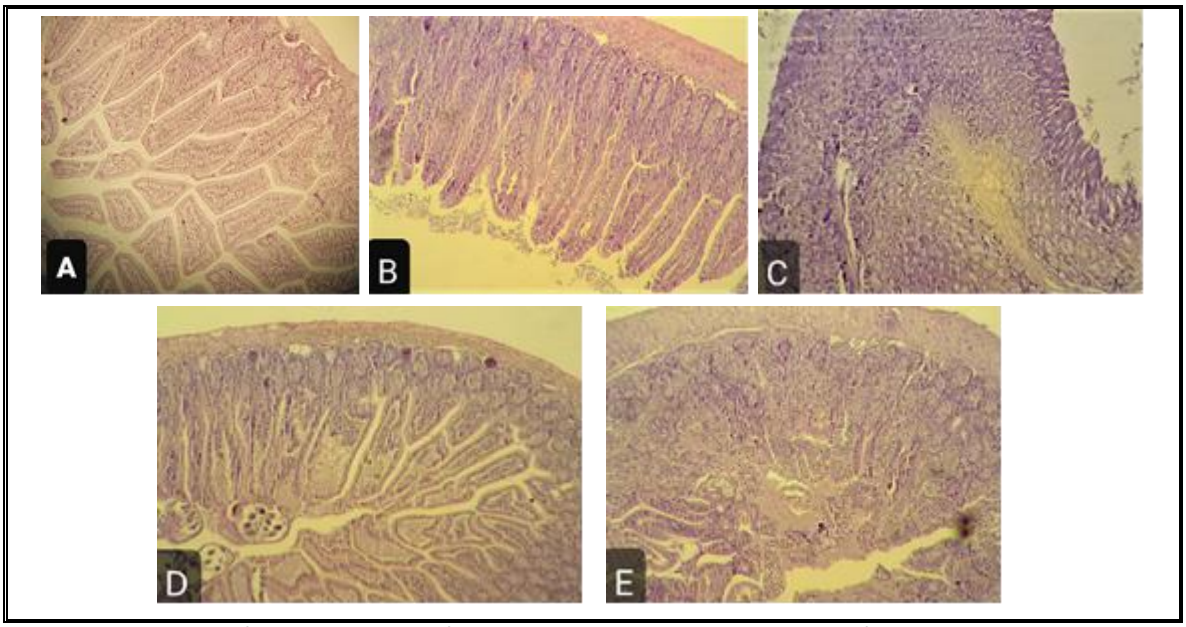

Figure 2. Histological sections of mouce intestine tissues from treated and non treated groups .(A) histology of normal control mouce intestine(X10) , (B) section from group treated with panadol showing look-like normal appearance of intestinal villi with mild inflammatory cells infiltration, (C) Section from mouce treated with ibuprofen showing dispersed slight shortening of intestinal villi with mild inflammatory cells infiltration , (D) section from group treated with ponstan showing widening of intestinal villi with inflammatory cells infiltration inside the villi, (E) section from group treated wih mix (panadol and ibuoprofen) showing intestinal villi hyperplasia with slight widening of villi .

Mucus and the value of pH are a natural barrier to both diffusion and absorption of foreign entities such as drugs, and these drugs or treatments may interact or interfere with the function of the intestinal mucous, hence this study was to find out the role of this type of antipyretics on this layer of the GI system. Ibuprofen, Ponstan and Panadol are the most commonly used for treating the pain and fever, and they are an over-the-counter (OTC) drugs [18], as we know the first tow drugs belong NSAIDs while panadol belongs analgesic drugs, so it needs regular evaluation of these drugs, We investigate the histological changes of Panadol, Ibuprofen, Ponstan and a combinations of Panadol and Ibuprofen in stomach and intestine tissues of the mice, and as we find there was an induction of histopathological abnormalities in these tissues, and when we compare this study with other studies the result agrees with Maria and their colleagues in 2018 in the sub mucosal hyperplasia of the gastric and dispersed slight shortening[19], hyperplasia with a widening of intestinal villi with mild inflammatory cells infiltration in the Ibuprofen, Ponstan and a combinations of Panadol and Ibuprofen groups while when using panadol group we found normal mucosal layer for gastric and intestine and this result agree with Bernard 2004[20].

NSAIDs are classified fundamentally into basic and acidic preparations Ito et al 1992, so Bjarnason, Rostom and Rao their colleagues in 2018, 2002 and 2000 confirmed that NSAIDs cause direct irritation of the gastric mucosa due to acidic activity which breaks the mucosa barrier and diffusion of acid into the mucosa and cause gastric ulcers[21-24], and also the inhibition of prostaglandin activity by uses of NSAIDs causes increased gastric acid secretion and decrease the ability of the gastric mucosal defence[25] , Ibuprofen found recently even in a short term use can induce gastric erosions and ulcers[26,27].

The demonstration from this result above that NSAIDs induced gastric histopathological abnormalities, this was confirmed by the single use of Ibuprofen and combination use of Ibuprofen with panadol from the appearance of the same histological changes on the gastric and intestine, this finding confirmed by Kalra and his colleagues in 2009 and Sostres and his colleagues in 2013 demonstrated these

drugs cause erosions, erythema, mucosal haemorrhage, and gastric or/and intestinal ulceration or perforation of lower GI and upper GI and events were frequent in these two places[28,29]. Many studies need to understand the wise use of NSAIDs to prevent serious complications.

CONCLUSIONS

NSAIDs are one of the most popular OTC drugs, for both adults and children. It has a good safety profile if used with precaution, as the adverse effect is infrequent. The side effect tends to appear more in patients high dose of NSAIDs for long duration. Specific precaution should be taken for the pediatric age group. Choosing Antipyretics should depend on the safety, efficacy, effectiveness, and duration of action. Also it's better to avoid combination of NSAIDs, as this increase the risk of complication.

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Not applicable.

Conflict of interest

The authors declare no conflicts of interest.

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