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Everted Intestinal Sacs As In vitro Model For Assessing Absorptivity Of L-Histidine Under The Effect Of Aspirine And Gum Acacia In Male Rats

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Abstract

The purpose of this study was to characterize intestinal permeability changes over a range of physiologically relevant intestinal injury. The experiments were performed in 80 rats subdivided into four groups as aspirin (400 mg/kg b.w.), gum Acacia (1g./day) and aspirin with gum Acacia groups for 21 days compared with control group. Relative reabsorption of L-Histidine was greater($p<0.001$) in the aspirin in 10 min of incubation compared with that of the control rats. In aspirin in combination with gum Acacia, the relative reabsorption were significantly ($p<0.001$) decrease in 10, 20 and 30 min. of incubation compared with that of the control rats. Moreover, the relative reabsorption of L-histidine was significantly ($p<0.01$) reduced by the aspirin at 45 min of time of the incubation buffer compared with that of the control. However, gum acacia treatment was increased at 10 min ($p<0.01$) ,30 min ($p<0.01$) and 45 min ($p<0.001$) respectively compared with that of the control rats. Relative reabsorption of L-histidine record a nonsignificant increase of aspirin at 20 min and 30 min of incubation compared with that of the control. Gum and aspirin with gum at 20min and 45min of incubation resulted an increase and decrease in relative reabsorption of L-histidine respectively compared with that of the control. Aspirin and aspirin in combination with gum acacia treatment increased body, intestinal weights and mucosal total protein significantly with percent changes ranged from 8% to 40% compared with that of the control. On the other hand, gum treatment decreased body, intestinal weights and mucosal total protein significantly with percent changes ranged from 8% to 35% compared with that of the control. These results demonstrated that L-histidine is actively taken up by a gum Acacia system in intestinal everted sac mechanism of rat with energy supplied by glucose and Na^+in incubation buffer. Moreover, aspirin system had an inhibitory effect on L-histidine uptake in 45 min of incubation , indicating the saturation by L-histidine in first ten minuts of incubation. Also, these results provide evidence the uptake of L-histidine into rat intestine was not reduced at all by the treatment of aspirin. These results suggest that the uptake of L-histidine by intestinal everted sac of rat has different characteristics of aspirin with gum compared with that of the control in respect to relative reabsorption of L-histidine.

Key words: everted sac, L-histidine,Aspirin, Gum arabic, relative reabsorption.

Introduction

Intestinal absorption of peptides were performed with the everted small intestine by Mizuma *et al.*,1992. The mucosa of gastrointestinal (GI) tract protects the internal gut lumen from bacteria and bacterial product such as endotoxin (Gisolfi, 2000). This protective feature of the gastrointestinal mucosa is referred to as GI barrier. Dysfunction of this barrier leads to an increase in intestinal permeability, which involves the passive, nonmediated diffusion of both small and large molecules from GI lumen to the blood (Travis and Menzies,1992). Increased intestinal permeability can result from numerous pathophysiological conditions including hemorrhage and endotoxemia (Salzman *et al.*,1994; Unno *et al.*,1997; Anand ***et***

al.,2004) and has been observed after strenuous exercise (Pals *et al*.,1997) and exercise combined with nonsteroidal anti-inflammatory drug use (Lambert *et al*.,2001; Ryan *et al*.,1996; Cui *et al.*,2004).

Aspirin, by virtue of its ability to irreversibly acetylate the cyclooxygenase enzyme, is capable of inhibiting both prostacyclin (PGI_2) production by endothelial cells (Abdel Salam *et al.*,1995). and thromboxane A_2 (TXA_2) synthesis by platelets(Buist,1984).At low doses of aspirin an antithrombotic environment can be created by the selective inhibition of TXA_2 (Dihlmann *et al*.,2001). Others would argue that both platelet and endothelial cyclooxygenases are equally inhibited, particularly after high doses or single administrations, or that any selectivity is a function of the route of administration (Thomas *et al*.,1993). **Sansom** *et al*.(2001) showed that dietary aspirin exposure can suppress tumorigenesis in the murine intestine and the mammary gland. Aspirin is a drug that reduces swelling, pain, and fever. In recent years, long-term low-dose aspirin has been recommended to reduce the risk of heart attacks and strokes. In the future aspirin may be recommended to reduce the risk of some cancers. Reye's syndrome, a rare but serious illness affecting children and teenagers, has been associated with aspirin use. To prevent Reye's syndrome, people should consult their doctor and/or pharmacist before giving aspirin, aspirin-containing products, or herbs containing salicylates to children and teenagers (Rees *et al.*, 1979).

Gastrointestinal (GI) bleeding is a common side effect of taking aspirin. A person with aspirin-induced GI bleeding may not always have symptoms (like stomach pain) or obvious signs of blood in their stool. Such bleeding causes loss of iron from the body. Long-term blood loss due to regular use of aspirin can lead to iron-deficiency anemia. Lost iron can be replaced with iron supplements. Iron supplementation should be used only in cases of iron deficiency verified with laboratory (Holzer *et al*.,1989). Taking aspirin has been associated with increased loss of vitamin C in urine and has been linked to depletion of vitamin C. People who take aspirin regularly should consider supplementing at least a few hundred milligrams of vitamin C per day. Such an amount is often found in a multivitamin (Coffey and Wilson,1975). Non-steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed drugs worldwide which attests to their efficacy as analgesics, and anti-inflammatory and anti-pyretic agents. The main concern with this group of drugs is the frequency and severity of their gastrointestinal side effects (Daneshmend *et al*.,1991) . Increased loss of folic acid in urine has been reported in rheumatoid arthritis patients (Buist,1984). Reduced blood levels of the vitamin have also been reported in people with arthritis who take aspirin (Alter *et al.*,1971). Also, Gastrointestinal (GI) bleeding is a common side effect of taking aspirin. A person with aspirin-induced GI bleeding may not always have symptoms (like stomach pain) or obvious signs of blood in their stool. Such bleeding causes loss of iron from the body. Long-term blood loss due to regular use of aspirin can lead to iron-deficiency anemia. Lost iron can be replaced with iron supplements. Iron supplementation should be used only in cases of iron deficiency verified with laboratory tests. Furthermore, Intake of 3 grams of aspirin per day has been shown to decrease blood levels of zinc (Ambanelli,1982). Aspirin appeared to increase loss of zinc in the urine in this study, and the effect was noted beginning three days after starting aspirin. The pathogenesis of intestinal damage is incompletely understood. It is generally accepted that the early pathogenic events include a "topical" phase in addition to the inhibition of cyclooxygenase, followed by a multistage pathogenic event in which intestinal permeability, luminal contents, neutrophils, and the microcirculation all play a role in the development of inflammation and ulcers (Whittle,1992a ; Wallace,1994; Rainsford & Whitehouse, 1982; Somasundaram *et al*.,1995). The importance of inhibition of cyclooxygenase in the damage induced by NSAIDs has been clearly documented (Whittle,1992b; Fiorucci ***et al.,*** 2004). Nevertheless, it is

possible to inhibit cyclooxygenase selectively without inducing intestinal damage (Levine *et al*.,1988; Ligumski *et al*.,1983; Ivey *et al*.,1980; Langenbach *et al.*,1995) . Furthermore, disruption of the prostaglandin synthase-1 gene coding for cyclooxygenase-1 in mice, with resulting mucosal prostaglandin concentrations of less than 1% of that of controls, is not associated with gastrointestinal pathology (Langenbach *et al.*,1995). In the stomach changes in drug formulation as enteric coating, rectal administration (Ivey *et al.*,1980; Rainsford, 1989) and abolishing gastric acid secretion induced damage (Daneshmend *et al*.,1991) presumably by limiting the gastric absorption of the drug greatly increase tolerability of NSAIDs in the short term. This suggests that the "topical" action of NSAIDs may be an important co-factor in the initiation of the damage (Whittle,1992a,b). The "ion trapping" hypothesis which postulates that accumulation of NSAIDs in intestinal epithelial cells depends largely on the interaction of the acidity of the NSAID (pKa) and luminal pH provides a basis for (along with molecular size, lipid solubility and contact time) the "topical" action of NSAIDs but not the mechanism (Brookes & Day, 1991; Brune *et al*., 1977; Kharasch ***et al***.,2004) . On the other hand, Gums are a high-energy food source composed mainly of water, complex polysaccharides, calcium, and trace minerals as iron, aluminum, silicon, potassium, magnesium, and sodium (Nash,1986). Calcium is important to all animals, especially female callitrichids (tamarins and marmosets) which commonly give birth to twins twice a year. It is during the lactation period that the females are usually impregnated by the male. The calcium-to phosphorus ratio is high in gums which offsets its ratio in insects, which is low. Because all known wild gummivores also include insects in their diet, combining the two, in captivity, may approach a desired nutritional balance and is recommended to avoid the possibility of nitrogen loss and the loss of protein from the body (Nash, 1986; Garber, 1984a; Sussman and Kinzey 1984; Coimbra-Filho, *et al*., 1978; Moynihan 1976). Furthermore, karaya gum does not disintegrate or decompose appreciably inthe alimentary tract. In a study of 10 dogs, 95% of the orally administered gum was recovered in the faeces. It absorbs a large quantity of water and therefore acts as a mechanical laxative. It tends to increase faecal nitrogen excretion, does not affect starch digestion in the dogs and does not inhibit the utilization of vitamin A in rats (Ivy & Isaacs, 1938). Five rats were fed karaya gum in the diet for two years. Three developed enlarged colon and ulceration (Carlson & Hoelzel, 1948). In another experiment, groups of three rats were fed karaya gum at first at 10%, gradually increasing to 25% in the diet over their life span. Controls of five and seven animals received low residue diets. No caecal ulceration was found in this experiment (Nash,1986).

Generally, animals that use plant exudates are small bodied, have a high metabolism, and are incapable of storing large amounts of fat. Primary gum-eaters have most, or all, of the following traits: small body size, clawed digits (for vertical clinging at gum sources), long procumbent or semi-procumbent incisors complimented by short lower canines (providing a level gouging/scrapping surface), loss of enamel on the lingual side of the lower incisors complimented by honing upper incisors (providing a sharpening effect that permits gouging or scraping abilities), a V-shaped configuration of the mandibular arch, a long tongue (to reach gums within the plant bark), and an enlarged cecum (to allow for fermentation of the gums) (Fleagle, 1988; Coimbra-Filho and Mittermier,1978; Rosenberger, 1978).

The transport characteristics of L-histidine through the blood-lung barrier were studied in cultured rat lung microvascular endothelial cells (LMECs). L-Histidine uptake was a saturable process. The addition of metabolic inhibitors [2,4-dinitrophenol (DNP) and rotenone] reduced the uptake rate of L-histidine. Ouabain, an inhibitor of Na^+-K^+-ATPase, also reduced uptake of L-histidine. Moreover, the initial L-histidine uptake rate was reduced by the substitution of Na^+ with choline chloride and choline bicarbonate in the incubation buffer (Sakurai et al.,2002**)**. However, the

plasma membrane of endothelial cells has been shown to be the site of several carrier-mediated transport systems (Shu *et al*.,1997; Yeh and Holt ,1986), including those for glucose, monocarboxylic acid, and amino acids. Three amino acids, L-glutamine, L-histidine, and L-asparagine, all of which have a nitrogen in their side group, are the natural substrates for this transporter (Hundal *et al.*,1987; Kilberg *et al*.,1980). In particular, L-histidine, an essential amino acid, is a precursor of histamine. Histamine initiates transitory increases in endothelial permeability *in situ* and *in vitro* (Moy *et al*.,1996, Wu and Baldwin, 1992). Under in situ conditions, increased permeability is associated with the development of small gaps between adjacent endothelial cells, and restored barrier function is associated with the reapposition of adjacent cells (Leach *et al.*,1995).

Materials And Methods

Male adult Sprague-Dawley rats, weighing 170–200 g, were used to study the intestinal absorption of L-Histidine by everted sac technique under the effect of aspirin, gum arabic and their combination. They were kept in a 12:12-h light-dark cycle and fed a standard chow diet ad libitum. Rats were placed on diets containing gum 1 g per day (Ivy & Isaacs,1938) followed by 400 mg/kg of aspirin (Sansom *et al*.,2001) for period 21 day . Control rats were placed on normal diet and water ad libtum.

Preparation of the everted sac: The everted sac technique described in detail by (Karasov and Diamond,1983). Rats were killed and open the abdomen by midline incision. Remove the small intestine by cutting each end . The middle small intestine were obtained from the proximal end. Wash the entire length of the small intestine with glucose-saline solution to remove blood, debrise. Insert a narrow glass rod into one end of the intestine. Tie a ligature over the thickened part of the glass rod and evert the sac by gently pushing the rod through the whole length of the intestine. Remove the rod and place the intestine in a glucose-saline solution at room temperature. Tie off 4 cm length of the intestine with thread and cut an open sac from the main length. Place asecond ligature loosely round the open end of the sac and introduce a blunt needle attached to a syringe.Tighten the loose ligature over the needle and inject 0.4 ml of the Krebs buffer L-glucose solution (in mM: 118 NaCl, 4.7 KCl, 25 $NaHCO_3$, 1.2 $CaCl_2$, 1.2 $MgSO_4$, 11.1 glucose, pH 7.4) for the concentration gradient experiments into the sac; tighten the ligature and withdraw the needle. All the ligtures have to be firm enough to prevent leaks but not tight so as damage the tissue. The total surface area of the everted sac of the small intestine were recorded.

L-Histidine transport: Immerse the sac in 15 ml of the 5 mmol/l histidine (BDH Chemicals,Ltd poole, England) solution bubbled with 95% O_2-5% CO_2, seal the flask and shake for 10 mi9n in 37 ^oC water bath. At the end of this time, analyse 0.2 ml of the solution inside the everted sac(mucosal side) for L-histidine after deproteinization. Repeat with other everted sacs after 20, 30 and 45 minutes.

Histidine measurement: Mix 1 ml of the weak acetic acid solution with 0.1 ml of test solution in a test tube, cover with a marble amd place the tubes in a boiling water bath for 10 min. Cool and add distilled water to give final volum of 2.5 ml and centrifuge. Take 1 ml of deproteinized solution, add 0.2 ml of sulphanilic acid (1 g/l in 1 mol/l HCl). Shake the tube and leave stand for 5 min with shaking. Add 0.6 ml of sodium carbonate solution7.5 (g/100ml) and shake vigorousy for about 10 second. Add 2 ml of ethanol(20%) and 1 ml of water, mix thoroughly and read at 498nm against distilled water after 30 min. Calculate the concentration of histidine present by reference to a standard curve of histidine concentration using 2 ml of 0.15mmol/l histidine instead of the 2ml of deproteinized fluid (Fenselau,1997) .

Relative Permeability =

Concentration $_{\text{serosal fluid}}$ x Volum $_{\text{serosal fluid}}$ ÷ mucosal surface area

Relative permeability: Flattened intestinal sacs were measured for length and width and surface area was calculated. Relative permeability (mmol/cm2 mucosal surface Determination of Intestinal total protein: Mucosal intestinal everted loop of known length was scraped with microscopic slide (Sharathchandra *et al*.,1995). The mucosal scrapings were homogenized in 0.9% saline and used for protein determination according to the method of Lowry *et al*.(1951) using bovine serum albumin as thestandard.

area) of everted sacs was calculated as transport of the L-histidine into serosal fluid on the basis of the following equation which indicated by (Lambert *et al*.,2002).
Statistical analysis: All values of tables from (1 to 4) are expressed as means for 5 rats. The uptake data in table (5 and 6) are presented as means ± SE of means for 5 rats. Comparisons of data among treated and control groups were carried out using student t'test according to (Snedecor and Cochran, 1969).

Table (1): Concentration of serosal fluid of L-histidine (mmol/l), mucosal surface area (cm^2) and relative permeability (mmol/cm^2) of intestinal everted sac under the effect of aspirin(400mg/kg b.w.) and Gum (5mg/kg b.w.) and their combination compared with that of the control male rats at 10 minuts time from the incubation.

Parameters	Control	Aspirin	Gum	Aspirin + Gum
Concentration of serosal fluid (Mean)	0.039	0.0189	0.0297	0.0174
Mucosal surface area (Mean)	4.42	3.564	3.388	4.252
Relative reabsorption (mmol/cm2)	0.00356	0.00214	0.0035	0.00164

. Means of five rats.

Table (2): Concentration of serosal fluid of L-histidine (mmol/l), mucosal surface area (cm^2) and relative permeability (mmol/cm^2) of intestinal everted sac under the effect of aspirin(400mg/kg b.w.) and Gum (5mg/kg b.w.) and their combination compared with that of the control male rats at 20 minuts time from the incubation.

Parameters	Control	Aspirin	Gum	Aspirin + Gum
Concentration of serosal fluid (Mean)	0.046	0.0341	0.0399	0.0208
Mucosal surface area (Mean)	4.472	3.44	3.538	3.84
Relative reabsorption (mmol/cm^2)	0.00428	0.0045	0.00464	0.00221

Means of five rats.

Table (3): Concentration of serosal fluid of L-histidine (mmol/l), mucosal surface area (cm^2) and relative permeability ($mmol/cm^2$)of intestinal everted sac under the effect of aspirin(400mg/kg b.w.) and Gum (5mg/kg b.w.) and their combination compared with that of the control male rats at 30 minuts time from the incubation.

Parameters	Control	Aspirin	Gum	Aspirin + Gum
Concentration of serosal fluid (Mean±S.E.)	0.056	0.0867	0.0796	0.0275
Mucosal surface area (Mean±S.E)	3.63	3.992	3.32	3.926
Relative reabsorption($mmol/cm^2$)	0.0062	0.00496	0.00996	0.00288

Means of five rats.

Table (4): Concentration of serosal fluid of L-histidine (mmol/l) , mucosal surface area (cm^2) and relative permeability ($mmol/cm^2$) of intestinal everted sac under the effect of aspirin(400mg/kg b.w.) and Gum (5mg/kg b.w.) and their combination compared with that of the control male rats at 45 minuts time from the incubation.

Parameters	Control	Aspirin	Gum	Aspirin + Gum
Concentration of serosal fluid (Mean±S.E.)	0.0664	0.0369	0.127	0.078
Mucosal surface area (Mean±S.E)	3.454	3.392	3.8	4.324
Relative reabsorption ($mmol/cm^2$)	0.0079	0.00439	0.0137	0.0075

Means of five rats.

Table (5): Relative permeability of intestinal everted sac under the effect of aspirin (400mg/kg b.w.) , Gum (5mg/kg b.w.) and their combination compared with that of the control of male rats at different times from the incubation (2, 4, 6 and 8 minuts). Mean ± S.E.

Parameters	10min.	20 min.	30 min.	45 min.
control (Mean±S.E.)	0.00356 ± 0.00018	0.0043 ± 0.00042	0.0062 ± 0.00041	0.0079 ± 0.00078
% Change	-	-	-	-
Aspirin (Mean±S.E)	0.00214± 0.000247 ***	0.0045 ± 0.0059 n.s.	0.00496 ± 0.00074 n.s.	0.00439 ± 0.00041 **
% Change	+39.89 %	+ 4.65 %	-20.00 %	-44.43 %
Gum (Mean±S.E.)	0.0036± 0.000115 **	0.00464 ± 0.0006 n.s.	0.00996 ± 0.00091 **	0.0137 ± 0.00088 ***
% change	+79.77 %	+7.91 %	+60.65 %	+73.42 %
Aspirin + Gum (Mean±S.E.)	0.00164± 0.0001 ***	0.00221± 0.000162 ***	0.00288± 0.000222 ***	0.0075± 0.00089 n.s.
% change	-53.93 %	-48.60 %	-53.55 %	-5.06 %

*Significant at P < 0.05 , ** high significant at P < 0. 01 , ***very highly significant at P < 0.001 and n.s. represent a nonsignificant respectively.

Table (6): Body weight (g), Intestinal weight (g)/10 cm length and Intestinal total protein (mg)/g tissue wt. under the effect of aspirin (400mg/kg b.w.) , Gum (5mg/kg b.w.) and their combination compared with that of the control of male rats. Mean ± S.E.

Parameters	Control	Aspirin	Gum	Aspirin+Gum
Body weight (Mean±S.E.)	181.2 ±1.91	201.6± 2.64***	166.6 ± 1.96***	196.0 ± 4.3**
% Change	-	+11.3 %	-8.1 %	+8.2 %
Intestinal weight (Mean±S.E)	0.46±0.0093	0.50 ± 0.005**	0.30 ± 0.016***	0.53± 0.02*
% Change	-	+7.76 %	-34.8 %	+14.22 %
Mucosal total protein/intestinal wt. (Mean±S.E.)	24.7± 0.49	34.6± 1.94***	20.0 ± 0.76***	29.4 ± 1.63*
% change	-	+40.08 %	-19.03 %	+19.03 %

*Significant at P < 0.05 , ** high significant at P < 0. 01 , ***very highly significant at P < 0.001 and n.s. represent a nonsignificant respectively.

Fig.(1): Relative permeability of intestinal everted sac of L -Histidine under the effect of Aspirin, Gum and their combination of male rats .

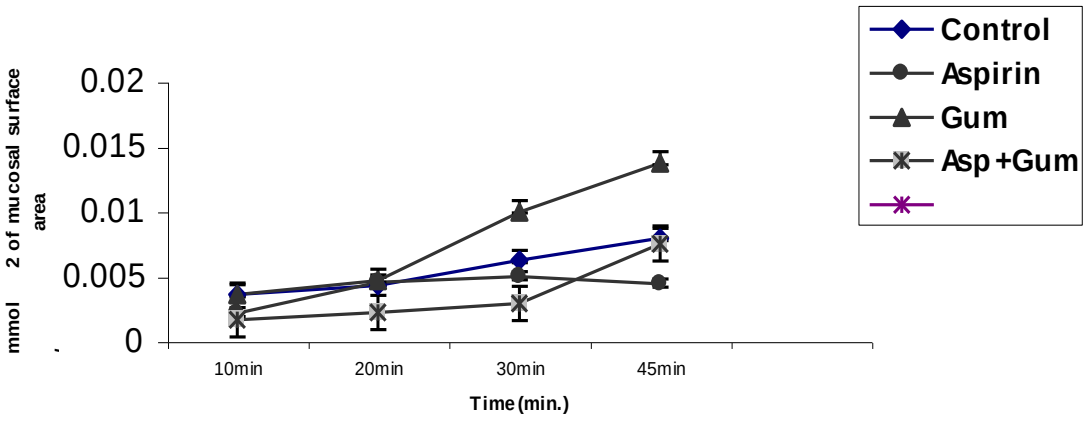


Fig.(2): Body weight and Mucosal total protein /g tissue weight under the effect of aspirin, gum and their combination of male rats.

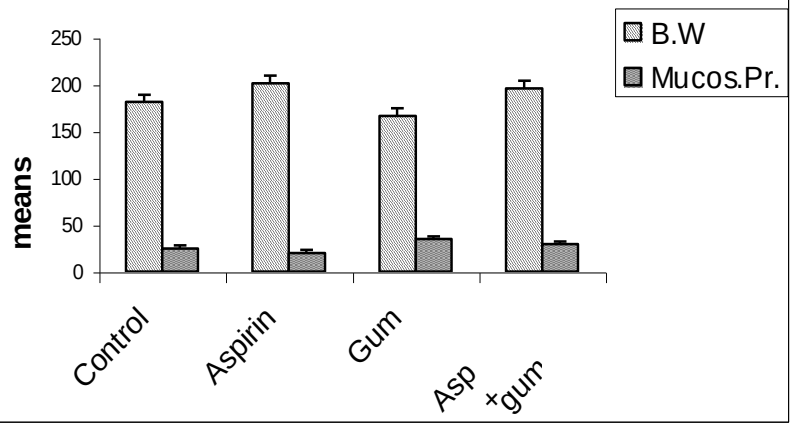
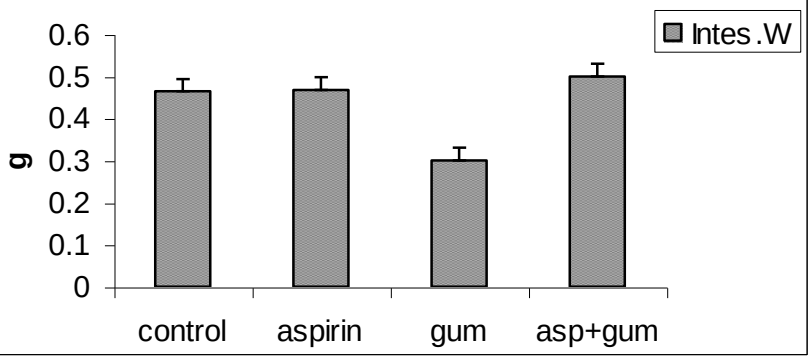


Fig.(3): Intestinal weight/10cm length under the effec of aspirin, gum and their combination in male rat



Results And Discussion

The effect of aspirin (400mg/kg body weight), gum and their combination on everted sac permeability is shown in (Table 1-5) and (Figure 1). Aspirin transport was significantly ($p<0.001$) increased above control levels at 10 min of incubation compared with that of the control. However, when the longer time (45 min) was used, permeability during this time was significantly ($p<0.01$) reduced below control levels. Control values were 0.00356±0.00018, 0.0043±0.00042, 0.0062±0.00041 and 0.0079±0.00078 mmol/cm^2 surface area at times 10, 20, 30 and 45 minuts of incubation respectively. The relative permeability of L-histidine under the effect of gum acacia were increased significantly at 10 min ($p<0.01$) and 30 min ($p<0.001$) above the control values. On the other hand, relative permeability of L-histidine under the effect of aspirin in combination with gum were reduced significantly ($p<0.001$) at 10 min, 20 min and 30 min of incubation respectively. Body and intestinal weights increased during the treatment of aspirin and aspirin in combination with gum and represented 11%, 8%, 7.7% and 14% respectively These were accompanied with the increase of mucosal total protein in aspirin and aspirin-gum groups by 40% and 19% respectively. On the other hand, gum treatment decreased body, intestinal weights and mucosal total protein significantly with percent changes ranged from 8% to 35% compared with that of the control (Table 6 and Figurs 2 -3).

The small intestine is the organ for nutrient absorption, which consists of digestion/metabolism and transport. Although the digestion/metabolism of dietary protein or peptides or oligo- or polysaccharides is required for absorption. medicinal drugs must be transported to systemic circulation without metabolic degradation to perform their pharmacological action. Membrane transportability is also expected to be low, since these compounds are hydrophilic and their molecular sizes are large. Therefore, the estimation of each process (metabolism and transport) is required for the evaluation of intestinal absorption. For the kinetic analysis of intestinal absorption, we proposed the metabolic inhibition model (Mizuma *et al*.,1996; Mizuma *et al* 1997), which can evaluate the intestinal absorption of analgesic peptides, leucine enkephalin and kyotorphin. The everted intestinal sac has been utilized for many years to study both absorption and permeability characteristics of intestinal tract. It has been modified over time to permit studies to be conducted on carbohydrate absorption (Crane and Wilson, 1958), drug absorption (Chowhan and Amoro, 1977) and permeability to other large molecules (Carter *et al.*,1990). Recently, Barthe *et al*.(1998) and **Anand *et al*.(2004)** reprted an improved method with greater viability of the sacs using cell culture medium rather than buffers for incubation and loading of the sacs.

Rats exposed to the aspirin diet gained weight normally when compared with rats on the control diet, and no ulceration or intestinal pathology such as perforation of the intestine was observed in any of the rats treated with aspirin. Two independent analyses were performed (**Sansom** *et al*.,2001). L-Histidine, an essential amino acid, is a precursor of histamine, an inflammatory mediator in the lung. Histamine activates local target cells and tissues, such as endothelial cells, fibroblasts, and smooth muscle (Hill,1990). L-Histidine uptake was a saturable process. Furthermore, addition of DNP or rotenone reduced the uptake rate of L-histidine, demonstrating that L-histidine uptake is metabolic energy dependent. Ouabain, an inhibitor of Na^+-K^+-ATPase, which is localized in the antiluminal membrane (Betz *et al*.,1980), also inhibited uptake of L-histidine, possibly by reducing the sodium gradient and membrane potential. The effect of ouabain suggested that one of the driving forces for L-histidine transport is Na^+, since choline did not substitute for Na^+. These results suggested that L-histidine is actively taken up by a carrier-mediated mechanism with

energy supplied by Na^+. Although the pathogenic events of NSAID induced gastrointestinal damage are controversial, there is a consensus that there is an important "topical" component of the damage both in the stomach and small intestine (Ivey *et al*.,1980; Ligumsky et al.,1982; Whittle,1992a) which is independent of NSAID action to inhibit cyclooxygenase (Baskin *et al.,* 1976; **Somasundaram** *et al*.,1997) .

The dual action of NSAIDs to uncouple oxidative phosphorylation-inhibit electron transport ("topical" action) and inhibit cyclooxygenase ("topical" and systemic action) provides a logical explanation for the mechanism and high prevalence of gastrointestinal toxicity of these drugs. Hence, uncoupling/inhibition following indomethacin (the precise site of absorption is in part determined by size, lipid solubility and charge of the NSAID, drug formulation, gastric pH, etc.) would result in diminished cellular ATP production, cellular calcium toxicity (Carefoli, 1987) , production of reactive oxygen species (Somasundaram *et al*.,1995) resulting in increased mucosal permeability (Bjarnason *et al.*,1989; Matthews *et al.*, 1994) . Increased intestinal permeability allows luminal aggressive factors access to the mucosa which results in an inflammatory reaction. The concomitant inhibition of cyclooxygenase (which occurs at picomolar concentrations of NSAIDs and hence evident irrespective of the mode of administration of the drugs), with decreased prostaglandins, may then alter local blood flow and therefore be an important cofactor in driving the inflammation to ulcers (Whittle,1992b; Somasundaram *et al*.,1995). Moreover, in an animal study, consumption of gum acacia stimulated intestinal and splenic immune system function (Eastwood et al.1986). The increases in absorptive capacities of protein by mucosal intestine is decleared by the growth of intestinal weight where this explanation was agreed with Buddington *et al*., 2001 explanation. Also, Ganapathy *et al*.(1994) indicated that the majority of dietary amino acids is apparently absorbed as component of peptides. Edwards *et al*.(1987) investigated the acute effects of guar gum on the bioavailability and utilization of dietary protein and to consider the possibility that gum might acutely modulate urea kinetics in humans. The viscosity of the meal was increased 100-fold, probably even more after ingestion because guar-gum-induced viscosity may develop in the stomach and may resist dilution and reneutralization more than viscosity induced by other gums .

Some studies reported that viscous fiber increases the gastric or intestinal secretion of fluids, specifically nitrogen, which indicates that guar gum may activate the upper intestinal disposal of urea (Marciani *et al*.,200 Rainbird and Low , 1986; Ehrlein and Stockmann,1998; Stephen and Cummings,1979).

In this experiment, in the treatment of aspirin at (400mg/kg b.w.) dose resulted in a progressive decrease in L-histidine uptake. This result also, suggested that gum acacia plays an important role in L-histidine uptake into rat intestinal everted sac. In summary, we have shown that dietary aspirin exposure can suppress permeability in the intestine. This effect seems to be specifically associated with a loss of function after the longer time of L-histidine incubation. Critically, in the intestine, suppression only becomes apparent if exposure covers the period between 30 min and 45 min of incubation after the saturated intestinal everted sac cells with L-histidine at 10 min of incubation.

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نموذج الكيس المعوي المقلوب خارج الجسم في تقييم امتصاص الهيستيدين تحت تأثير عقار الأسبرين وصمغ أقاقيا في ذكور الفئران البيضاء

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تم في هذا البحث دراسة الامتصاص المعوي للهستيدين في الفئران بإستخدام تقنية الكيس المعوي المقلوب خارج جسم الحيوان تحت تأثير بعض التغيرات الفسيولوجية المستحدثة بعقار الأسبرين والصمغ أقاقيا. أستخدم في هذا البحث ثمانون فأر أبيض كبير بأوزان تتراوح من 170 الي 200 جم وقد قسمت الي مجموعات وتتكون كل مجموعة من عشرون فأر وهي كالآتي:

مجموعة الأسبرين: وقد استخدم الأسبرين بجرعة 400 ملجم/كجم من وزن الجسم تم تناوله بالفم مع الغذاء لمدة 21 يوما علي التوالي.

مجموعة الصمغ: وتم أستخدام الصمغ بجرعة 1 جرام يوميا مع الغذاء لمدة 21 يوما علي التوالي.

مجموعة الصمغ والأسبرين:أستخدمت نفس الجرعات السابقة ولمدة 21 يوما متتاليا فميا مع الغذاء.

المجموعة الضابطة: لم يتم في هذه المجموعة أي اضافات دوائية للغذاء أو الماء.

و تم تقسيم كل مجموعة تبعا للوقت الذي تم دراسة الإمتصاص الي أربعة مجموعات 10، 20، 30، 45 دقيقة علي التوالي و كل مجموعة تتكون من خمسة فئران. في نهاية التجربة تم تخدير الحيوان وعمل شق طولي بالبطن ثم قطع طول معين من الأمعاء وتفريغه وتنظيفه بمحلول منظم معلوم درجة تركيزه الأيوني. يتم قلب الكيس المعوي بواسطة ربط أحد أطرافه بساق زجاجية بحيث يكون السطح المخاطي الي الخارج والسطح المصلي الي الداخل . يربط أحد الأطراف ويتم ادخال سرنجة بدون ابرة مملوئة بمحلول منظم يحتوي علي جلوكوز وصوديوم الي الطرف الآخر ويتم الربط إحكام بدون ايتلف في النسيج المعوي. يوضع هذا الكيس في كأس يحتوي علي تركيز معلوم من الهيستيدين المراد قياس معدل إمتصاصه بعد 10، 20، 30، 45 دقيقة من بدأ التحضين مع توفير درجة حرارة مناسبة وتوفير اكسجين مع ثاني أكسيد الكربون . وفي نهاية كل وقت يتم تعيين تركيز نسبة الهيستيدين الممتص داخل الكيس وقياس طول وعرض الكيس المعوي وتعيين مساحته ثم يتم تعيين معدل الإمتصاص بالمعادلة المذكورة من قبل في المواد والطرق بداخل البحث وكانت النتائج كالتالي: في الحيوانات المعالجة بالأسبرين كان هناك زيادة واضحة($p<0.001$) في معدل الإمتصاص في العشرة دقائق الأولي من التحضين مصاحبة لنقص ملحوظ($p<0.01$) بعد 45 دقيقة من بداية التحضين مقارنه بالمجموعة الضابطة. بالنسبة للأسبرين والصمغ أقاقيا معا كان هناك نقص ملحوظ ($p<0.001$) بعد 20،10، 30 دقيقة من التحضين مقارنة بالمجموعة الضابطة بالنسبة للمعالجة بالصمغ فقط فكان هناك زيادة ملحوظة بعد 10($p<0.01$) دقائق و 30 ($p<0.01$) دقيقة و 45 ($p<0.001$) دقيقة مقارنة بالمجموعة الضابطة علي التوالي. أيضا سجلت النتائج زيادة ملحوظة في وزن الجسم ووزن 10 سم من الأمعاء في الحيوانات المعالجة بالأسبرين وكذلك الأسبرين مع الصمغ في نسب التغير المئوي تتراوح من 7% الي 11% ز أيضا وجد أن هناك زيادة معنوية في البروتينات الكلية للطلائية لكل كيلو جرام من وزن المعي في مجموعة الأسبرين و مجموعة الأسبرين مع الصمغ وتراوحت الزيادة من 19% الي 40% في نسبة التغير. علي الجانب الآخر سجلت مجموعة الصمغ فقط نقصا ملحوظا في وزن الجسم والأنبوب المعوي لكل 10 سم والبروتين الكلي من 8% الي 53% في نسبة التغير. ومن هذه النتائج يتضح أن الأسبرين لا يمنع الإمتصاص المعوي للهيستيدين بصورة مطلقة ولكن الأسبرين مع الصمغ أقاقيا له خوا ص فسيولوجية مختلفة مقارنة بالمجموعات الضابطة.