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A Comparative Study upon the Cytoprotective Effect of Prostaglandin F2α and Acetaminophen on Indomethacin and Absolute Alcohol-induced Gastric Damage in Rat

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Abstract: This study was undertaken to investigate the comparison of the ability of a cytoprotective synthetic PGF2α and acetaminophen, to protect rat gastric mucosa against indomethacin and absolute alcohol. Fasted male rats received intragastric pretreatment of acetaminophen or either orally or IP PGF2α 30 min prior to either indomethacin (20 mg kg^{-1}, oral suspension) or 1 mL of orally administered absolute alcohol. In another series of experiments rats were given acetaminophen concurrently with oral suspension of indomethacin or absolute alcohol. The animals were scarified 1 or 5 h after absolute alcohol or indomethacin administration respectively and the gastric mucosa was assessed for gross necrosis and for histologic changes. The results of this study showed that pretreatment with acetaminophen or PGF2α significantly reduced gross histologic changes and deep histologic necrosis versus control group. Co-administration of acetaminophen produced reduction in gastric lesions significantly, but this effect was less than when administered 30 min prior to indomethacin or absolute alcohol. The data obtained indicated effective protection of the gastric mucosa against ethanol and indomethacin injury can be achieved by oral administration of acetaminophen, probably through stimulation of gastric prostaglandins secretion.

Key words: Gastric lesions, indomethacin, alcohol, PGF2α, acetaminophen, cytoprotection

INTRODUCTION

Acetaminophen (paracetamol) is perhaps the most widely used analgesic/anti-pyretic drug throughout the world. Unlike Non-Steroidal Anti-Inflammatory Drugs (NSAID), acetaminophen is not only having an anti-inflammatory activity but considered to be safe on gastric mucosa (Lanza *et al*., 1998; Ivey *et al*., 1978) and also it has been shown to reduce the gastric injuring side effect of indomethacin (Van Kolfschoten *et al*., 1982) and other gastric injuring agents such as aspirin and alcohol in rat (Seegers *et al*., 1979) and in acute exposure in human (Stern *et al*., 1984). However, other studies failed to demonstrate this action in dog (Leeling *et al*., 1981) and in chronic studies in man (Graham and Smith, 1988).

Since these early studies in the 1980s, this aspect of acetaminophen has been overlooked. The few studies that were conducted evaluated the cytoprotective action of acetaminophen by use of different parameters ranging from macroscopic (Van Kolfshoten *et al*., 1983) to measurement of prostaglandin release (Van Kolfschoten, *et al*., 1982) or scanning electron microscopy (Ohno *et al*., 1985). The mechanism by which acetaminophen produces its cytoprotective action is still unknown, but suggested to involve prostaglandin release, stimulation of the inhibited local biosynthesis of protective prostaglandins or directly activate protective factors in the gastric mucosa and mucus or bicarbonate secretion (Van Kolfscholten *et al*., 1982).

On the other hand, there are ample of evidences that prostaglandins do have cytoprotective action on gastric mucosa (Brzozwski *et al*., 2005). They are believed to act via reduction of acid release (Robert *et al*., 1968) or activation of other gastro-protective mechanisms (Robert *et al*., 1979). However none of the previous studies have used an *in vivo* method of assessing the degree of cytoprotective effects of acetaminophen when administered simultaneously with indomethacin or absolute alcohol, two agents known to produce gastric erosion. This type of protocol is important because it can give an indication of possible direct cytoprotective action of acetaminophen.

The aims of this study were, therefore, to assess the effectiveness and elucidate the possible mechanisms of cytoprotection produced by acetaminophen under various experimental conditions following both co-administration and prior to indomethacin and absolute

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alcohol, using both macroscopic and microscopic methods. The degree of cytoprotection was compared with those obtained following PGF2α administration. This study is unique in its protocol in that it simultaneously measures and compares the effectiveness of acetaminophen with that of prostaglandin against two known damaging agents. In addition, it employs co-administration of acetaminophen with either indomethacin or alcohol, a method that was not applied previously. This was undertaken to assess the onset of action of cytoprotective effects of acetaminophen prior to inhibition of prostaglandins by indomethacin or at commencement of the non-specific damaging effects of alcohol.

MATERIALS AND METHODS

Animals: N-Mari rats (Hassarak, Karaj, Iran) of either sexes (average weight 200 g), were randomly selected and divided into 11 groups of 5 animals each. The animals were housed in polystyrene cages with perforated stainless steel flat bottoms to allow ventilation and prevented the ingestion of faeces. Prior to experimentation, the animals had free access to food (Khorak-e-Dam, Shoshter, Iran) and city tap water. The lighting conditions were on 12 hourly basis and temperature conditions of 24±2°C. These experiments were carried out in the faculty of pharmacy of Ahwaz Jundishapur University of Medical Sciences, Iran The animals were withheld from food, but had free access to water over 24 h prior to drug administration. This project was approved by the ethical committee of research affairs of School of Pharmacy of Ahwaz Jundishapur University of Medical Sciences, in 2003. This research was carried out in the Pharmacology Department of Ahwaz Jundishapur University of Medical Sciences.

In these *ex-vivo* experiments used both macroscopic and microscopic evaluation of the effectiveness of acetaminophen and prostaglandin F2α (PGF2α) on both indomethacin and absolute alcohol-induced gastric damage.

The protocol of these experiments are divided into the following sections:

Induction of gastric lesions by indomethacin and absolute alcohol: In order to show the inductivity of gastric lesions by indomethacin and absolute alcohol, three groups of five rats were used. The gastric erosive effects of oral indomethacin in 1% carboxymethylcellulose suspension (20 mg kg^{-1}) and absolute alcohol (1 mL, orally) were assessed and compared with control normal saline-treated rats.

Comparison of oral and IP route of PGF2α on indomethacin and absolute alcohol: In this set of experiments, four groups of five rats were utilized. Indomethacin or absolute alcohol at the same dose as above, were administered thirty minutes after an oral or IP administration of PGF2α (2.5 mg kg^{-1}) (Chemical formala Lutalyse, Upjohn, Belgium).

Assessment of effectiveness of acetaminophen on indomethacin and absolute alcohol-induced gastric lesions: Two groups of five rats were used and administered, orally, acetaminophen suspension in 1% carboxymethylcellulose (250 mg kg^{-1}) 30 min prior to administration of 20 mg kg^{-1} indomethacin suspension or 1 mL oral absolute alcohol.

Assessment of onset of action of acetaminophen on indomethacin and alcohol-induced gastric lesions: To determine if the onset time for cytoprotection produced by acetaminophen was dependent upon the gastric damage that induced by prostaglandin inhibition, or was conducted via other mechanisms, acetaminophen was co-administered with oral suspension of indomethacin or absolute alcohol. Therefore, in this set of experiments two groups of five rats were co-administered, orally, 250 mg kg^{-1} acetaminophen suspension with either 20 mg kg^{-1} indomethacin or 1 mL absolute alcohol.

All the animal groups were sacrificed after 5 h by exposure to an over dose of ether and neck dislocation 5 h after indomethacin or 1 h after absolute alcohol dosing. The stomachs were removed and cut at the greater curvature and washed with normal saline and pin fixed on a wooden base. For macroscopic evaluation, the lesions were counted using a hand held magnifier by an independent observer, who was unaware of the treatment given and the largest length of each lesion was measured to the nearest millimetre. The therapeutic index, reflecting in percentage of reduction in the extent of development of lesions were calculated using the following relationship:

$$\text{Therapeutic Index} = \frac{\text{Positive control} - \text{Treament group}}{\text{Postive control}} \times 100$$

Where, positive and treatment group values are the mean lengths of the lesions for indomethacin or absolute alcohol (positive controls) and PGF2α or acetaminophen-treated are treatment groups, respectively (Table 2).

Gastric specimens, obtained in standardized fashion (Tarnawski *et al*., 1985) containing the entire

length of the oxyntic mucosa, were fixed in 10% buffered formalin and stained with hematoxylin and eosin.

For microscopic method the criteria for scoring and assessment of damage and cytoprotection for each treatment, was adopted as that suggested by Lacy and Ito (1982) and summarized in the Table 1.

Table 1: Criteria used for assessment of depth of injury and repair

Type of damage/repair	Criteria
Normal	No damage present
Type 1 damage	Damage of epithelial surface mucus cells only
Type 2 damage	Damage to epithelial surface and gastric pit surface mucus cells
Type 3 damage	Damage to epithelial surface and pit gastric surface cells plus injury of upper gastric gland cells
Type 4 damage	Presence of necrotic lesions. Severe mucus injury to all epithelial and pit surface mucus cells plus most or all gastric gland cells
Repair	Luminal surface and/or pit lining cells characterized by basophilic attenuated cytoplasm and flattened nuclei.

Statistical analysis: Quantitative data were analysed by one way ANOVA followed by post hoc Tukey methods and levels below 5% were considered statistically significant.

RESULTS

Macroscopic assessments: Both indomethacin and absolute alcohol produced lesions that were found in the mucosa and consisted of elongated bands ranging from 1-10 mm long by 1-3 mm wide (Fig. 1a and b). These lesions were usually parallel to the long axis of the stomach. Usually 15 to 25 lesions could be counted and located mostly in the corpus, while the antrum was less affected. No gross lesions could be seen in the forestomach (the non secreting part of the stomach). Table 2 and 3 summarize the results of various treatment groups. No lesions were observed in the normal

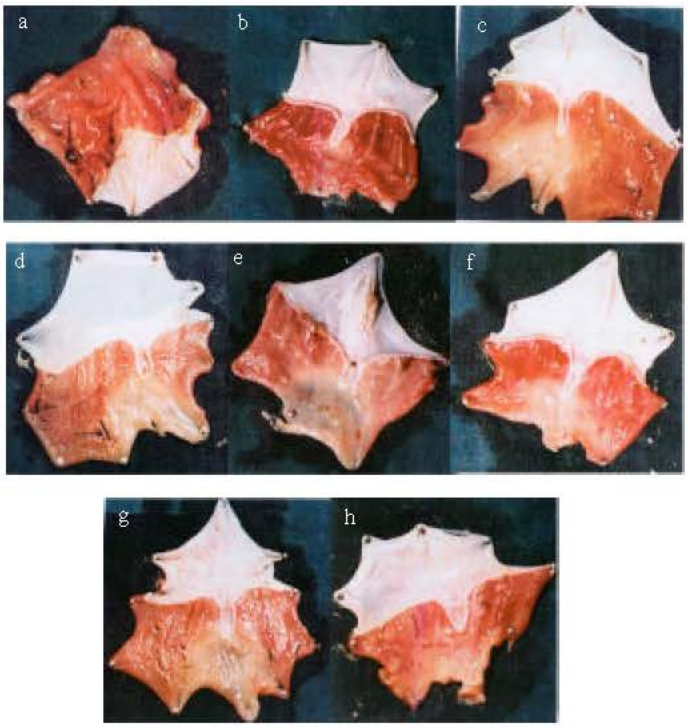

Fig. 1: Gross appearance of the gastric mucosa. (a) At 5 h after 20 mg kg^{-1} indomethacin administration orally. (b) Stomach of a rat 1 h after 1 mL absolute alcohol treatment. (c) Protection by pretreatment with PGF2α (2.5 mg kg^{-1}) given orally 30 min before indomethacin. (d) Protection by pretreatment with 250 mg kg^{-1} acetaminophen given orally 30 min before indomethacin. (e) Cytoprotective effect of acetaminophen on gastric mucosa when administered simultaneously with indomethacin. (f) Prevention of ethanol induced gastric ulceration by PGF2α. (g). Gastric cytoprotection by acetaminophen. Protection is seen by pretreatment with acetaminophen, given orally 30 min before ethanol administration. (h). Prevention of ulcerogenic effect of absolute alcohol by co-administration of acetaminophen

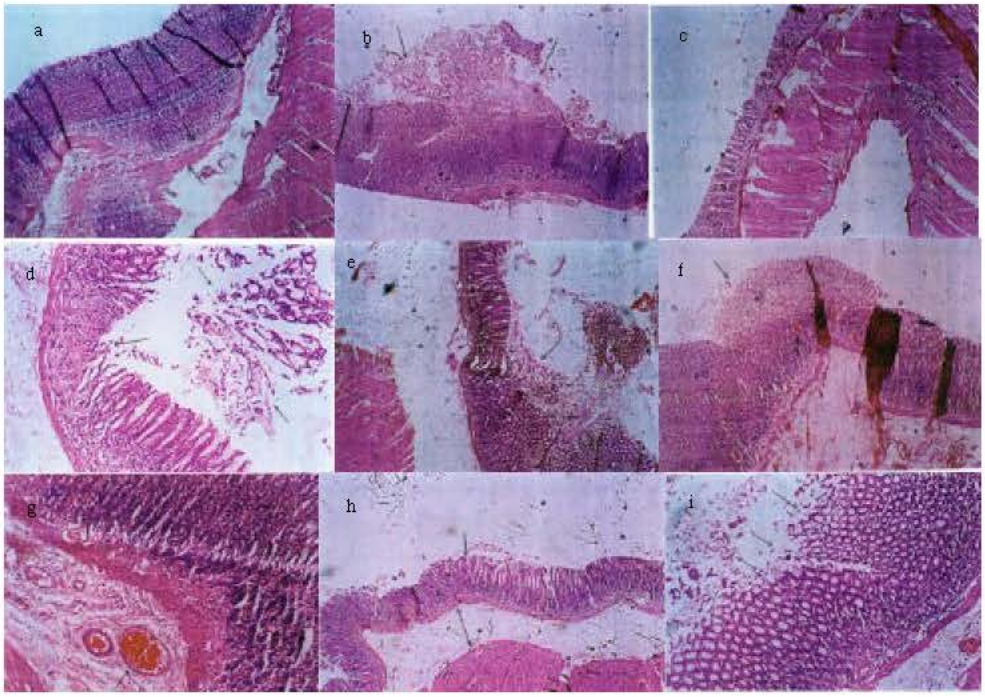

Fig. 2: Histologic appearance of the gastric mucosa. (a) In normal control rat (b) Five hours after indomethacin administration. Deep mucosal necrosis and edema of the submucosa are present (c) Pretreatment with acetaminophen given orally 30 min before indomethacin administration. Deep histologic necrosis of the gastric mucosa and microvascular damage, were absent or minimal (d) Protection by pretreatment with PGF2α given orally 30 min before indomethacin administration. Superficial mucosal necrosis but not edema of submucosal is seen (e) Simultaneous administration of acetaminophen and indomethacin. Deep mucosal necrosis and edema of the submucosa is prevented but a superficial necrosis is evident (f) One hour after ethanol administration Deep hemorrhagic lesions penetrating through the entire mucosal thickness is seen (g) Thirty min after ethanol and ministration in rats pretreated with orally PGF2α. Mucosal necrosis is completely prevented but slightly edema anleukocytic infiltration of submucosa is noticed (h) Co-administration of ethanol and acetaminophen. Deep histologic necrosis of the gastric mucosa and microvascular damage, are absent or minimal, the surface epithelium is mostly continuous, but submucosal edema is lightly present. (i) Thirty min after ethanol administration in rat pretreated with acetaminophen. The gastric mucosa showed only minimal necrotic lesions

saline-treated control group. The overall observation showed that both PGF2α and acetaminophen were effectively and significantly reduced the erosive effects of both indomethacin (Table 2) and absolute alcohol (Fig. 1c, d, f and g). PGF2α (Table 3) had the highest therapeutic index (percentage of protective effect) in both treatment groups. While, acetaminophen co-administered with both indomethacin (Table 2) and absolute alcohol (Table 3) had the lowest therapeutic index (percentage reduction) among the other groups (Fig. 1e and h).

Microscopic results: One hour after ethanol and 5 h after indomethacin administration the rats had severe haemorrhagic necrosis involving the glandular gastric mucosa in comparison to the normal controls (Fig. 2a, b and f). In contrast in the rats pre-treated with oral and intraperitoneal PGF2α, indomethacin and absolute alcohol induced only minimal necrotic lesions of gastric mucosa (Fig. 2d and g). The results of this study also showed that pre-treatment with acetaminophen significantly reduced damaging effects of indomethacin and ethanol on gastric mucosa (Fig. 2c and I). We also noticed that simultaneous use of acetaminophen with indomethacin and ethanol prevented the destructive effects of both necrotizing agents on the gastric mucosal layer (Fig. 2 e and h).

Table 2: The macroscopic results for the effectiveness of oral and IP PGF2α (2.5 mg kg^{-1}) and 3acetaminophen (250 mg kg^{-1}) co-administered with and 30 min prior to 20 mg kg^{-1} oral indomethacin suspension in reducing the of gastric lesions in rat

Treatment groups	Mean±SEM Length	Reduction (%) (Therapeutic index)
Indomethacin (20 mg kg^{-1})	16.2±0.96	0.0
PGF2α (2.5 mg kg^{-1}) oral	5.2±0.80	67.7*
PGF2α (2.5 mg kg^{-1}) IP	4.8±1.24	70.2*
Acetaminophen (250 mg kg^{-1}), 30 min prior to indomethacin	6.0±1.22	62.9*
Acetaminophen (250 mg kg^{-1}), co-administered with indomethacin	7.0±1.00	55.0*

PGF2α: Prostaglandin F2α; *p<0.05 relative to indomethacin, one way ANOVA followed by Tukey post hoc test

Table 3: The macroscopic results for the effectiveness of oral and IP PGF2α (2.5 mg kg^{-1}) and acetaminophen (250 mg kg^{-1}) co-administered with and 30 min prior to 1 mL absolute alcohol in reducing the of gastric lesions in rat

Treatment groups	Mean±SEM Length	Reduction (%) (Therapeutic index)
Absolute alcohol (1 mL)	12.2±1.35	0.0
PGF2α (2.5 mg kg^{-1}) oral	3.8±1.00	68.8*
PGF2α (2.5 mg kg^{-1}) IP	3.4±1.32	72.1*
Acetaminophen (250 mg kg^{-1}), 30 min prior to absolute alcohol	4.0±1.14	67.1*
Acetaminophen (250 mg kg^{-1}), co-administered with absolute alcohol	5.5±0.25	59.0*

PGF2α: Prostaglandin F2α; *p<0.05 relative to absolute alcohol, one way ANOVA followed by Tukey post hoc test

DISCUSSION

Since their discovery, prostaglandins have been implicated as house keeping agents in various tissues throughout the body systems. Early studies reported that prostaglandins produced their favourable protective effects on the gastric mucosal were due to their acid anti-secretory action (Robert, 1968; Robert *et al*., 1968). However, the same author (Robert *et al*., 1979), showed that prostaglandins were effective in preventing ulcer formation by a variety of damaging agents to be independent of their acid anti-secretory action.

On the other hand, the general assumption made is that inhibition of prostaglandin synthesis leads to gastric ulceration and administration of prostaglandins can prevent this action. However, the precise role of prostaglandins in this preventive effect is not known for certain. It was earlier suggested to be mediate by acid inhibition, which was later disputed to be independent of this action. Furthermore, another term was coined (adaptive cytoprotection) was attributed to cytoprotection that was produced by mild irritants such as 20% alcohol (Chaudhury and Robert, 1980). Even these studies attributed this protection to the release of prostaglandins. We present evidence that prevention of gastric necrosis is not mediated directly to prostaglandins.

Prostaglandins are classified as autacoids that are released by a variety of tissues through out the body, where they exert their actions locally. Among the many sites that are produced is the epithelial cells of the stomach, where they influence the play a role in the gastrointestinal physiology (Bennett, 1976). Furthermore, they have been implicated in the cytoprotection of the stomach against injury induced by a variety of damaging agents (various studies). However, the exact mechanisms by which prostaglandins induce their cytoprotective effects are still unknown. They have been suggested to exert their effects independent of their inhibitory effects on acid secretion (Robert, 1977).

Previous *in vivo* experiments showed that acetaminophen reduced the injuring side effects of indomethacin. This action was attributed to pharmacodynamic action on the mucosal cells rather than its physiochemical interaction (Van Kolfschoten *et al*., 1982) this finding resulted in proposal that acetaminophen cytoprotective effects to be mediated by local production of protective prostaglandins. However, Romano *et al*. (1988) demonstrated, in an *ex vivo* monolyer human gastric epithelial cell culture, that cytoprotective action of acetaminophen was not conferred via prostaglandin production. However, acetaminophen failed to prevent the mucosal injury of ibuprofen when given over several days (Lanza *et al*., 1986). These contrasting conclusions suggest that acetaminophen protective actions to be mediated via activation of other protective mechanisms in addition to its prostaglandin production. Later studies contested the general term of cytoprotection to be solely to macroscopic observations and further histological investigations demanded that this term can only be due to prostaglandin production. The findings from present study demonstrated that acetaminophen confers cytoprotection when administered 30 min prior to indomethacin and absolute alcohol as well a s when co-administered with these agents. Thus it seems that acetaminophen has a dual action of direct as well as an indirect protective effect against both these erosion-producing agents.

Prostaglandin E2 was demonstrated in the reduction of alcohol-induced gastric damage, but no exact role for the mechanisms responsible for this action was fully elucidated (Robert *et al*., 1979). They suggested involvement of the sparing of cellular pool in the gland isthmus from damage, enhancement of cellular migration from this pool to resurface the damaged epithelium or a combination of both of these processes. The results from present study demonstrated that the route of administration of PGF2α to have marginal non-significant effect (p>0.05) on the degree of its cytoprotective activity.

In fact, the IP route was approximately 2 to 4% more effective than the oral route, suggesting that the cytoprotective effects conferred by PGF2α was not dependent upon its direct contact with the mucosa.

Bicarbonate secretion induced by exogenous prostaglandin administration has been well demonstrated in oxyntic glandular region of the canine stomach when studied *in vivo* conditions (Miller *et al*., 1983). Under normal conditions, alcohol induced immediate damage to rat glandular gastric surface, which was followed after 3 min with a repair process which was complete within 60 min (Lacy and Ito, 1982). This rapid effect could not be demonstrated in another study (Schmidt *et al*., 1987), may be due to prolonged and profound injury induced by ethanol in their study, which required a longer period for epithelial reconstitution to occur.

Various gastric erosive agents induced damages via different mechanisms; this was observed by the differences in the degree of protection demonstrated with acetaminophen (Van Kolfschoten *et al*., 1983). The reasons for these differences may be related to the degree of inhibition of prostaglandins that the offending agents produce, for example aspirin is known to induced irreversible inhibition, while those produced by indomethacin are reversible.

Whether acetaminophen protected the stomach only against the injury produced by all NSAIDs or also against non-specific injurious agents such absolute alcohol is still a matter of debate. Mild gastric irritants, such as dilute ethanol (Van Kolfschoten *et al*., 1983) and 10% sodium chloride (Danon and Assouline, 1979; Van Kolfschoten *et al*., 1983) have been shown to protect the stomach against irritants. Furthermore, although from the findings of present study we showed that acetaminophen has both direct and indirect cytoprotective action when administered orally, it can not confer protection against every gastro-erosive agent when administered subcutaneously in rat (van Kolfschoten *et al*., 1982) or when given over a prolonged period with aspirin in human subjects (Graham and Smith, 1985).

The overall findings from this study demonstrates that acetaminophen is a useful cytoprotective agent when given administered both simultaneously and prior to an offending agent such as alcohol or indomethacin However, its exact cytoprotective mechanism is still unknown and further research is prudently needed to elucidate this mechanism.

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