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Evaluation of anti-ulcerogenic and ulcer-healing activities of nevirapine in rats

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Abstract

Background: Nevirapine is a very potent antiretroviral drug frequently used in the management of Human Immunodeficiency Virus (HIV). Opportunistic pathologies in HIV/AIDS patients include gastric ulcer and gastrointestinal haemorrhage. Hence, the impact of nevirapine on induced gastric ulcer was studied using Wistar rats.

Methods: Anti-ulcer activity of nevirapine was evaluated using cold restraint stress-induced, ethanol-induced and pylorus ligation-induced gastric ulcer models for acute ulceration; and acetic acid-induced ulcer model for the chronic ulceration in Wistar rats.

Results: Nevirapine (9mg/kg, 18mg/kg and 36mg/kg) showed significant ($P<0.05$) reduction in ulcer severity score and ulcer index as compared to the control in the models, with corresponding increase in percentage inhibition. Histopathological studies showed that nevirapine has a positive effect on the healing of gastric ulcer in the groups treated with the nevirapine compared with the control. The induced ulcers healed up in all the groups administered with nevirapine compared to what was found in the omeprazole group where manifestations of ulcer like inflammatory cells infiltration is still present.

Conclusion: Nevirapine may possess highly therapeutic effect in the treatment and prevention of gastrointestinal complications that might come with the presence of HIV virus in patients

Keywords: *Nevirapine, gastric ulcer; anti-ulcer; ulcer-healing, omeprazole, ranitidine.*

Résumé

Contexte: La névirapine est un médicament antirétroviral très puissant fréquemment utilisé dans la gestion du virus d'immunodéficience humain (VIH). Les pathologies opportunistes chez les patients atteints du VIH / SIDA comprennent l'ulcère gastrique et l'hémorragie gastro-intestinale. Ainsi, l'impact de la névirapine sur l'ulcère gastrique induit été étudiée en utilisant des rats Wistar.

Méthodes: L'activité anti-ulcère de la névirapine a été évaluée à l'aide de retenue froid des modèles d'ulcère gastrique induits par le stress, par l'éthanol et par ligature pylore pour l'ulcération aiguë; et le modèle d'ulcère induite par l'acide acétique pour l'ulcération chronique chez les rats Wistar.

Résultats: La névirapine (9 mg / kg, 18 mg / kg et 36 mg / kg) ont montré une réduction significative ($P<0,05$) du score de gravité de l'ulcère et indice d'ulcère par rapport au témoin dans les modèles, avec augmentation correspondant dans le pourcentage d'inhibition. Les études histo-pathologiques ont montré que la névirapine a un effet positif sur la guérison de l'ulcère gastrique chez les groupes traités avec la névirapine par rapport au témoin. Les ulcères induits guéris dans tous les groupes avec la névirapine par rapport à ce qui a été trouvé dans le groupe oméprazole où des manifestations de l'ulcère comme infiltration de cellules inflammatoires est toujours présent.

Conclusion: La névirapine peut posséder effet hautement thérapeutique dans le traitement et la prévention des complications gastro-intestinales qui pourraient survenir avec la présence du virus VIH chez les patients

Mots-clés: *névirapine, ulcère gastrique, anti-ulcère, guérison d'ulcère, oméprazole, ranitidine*

Introduction

An ulcer is a crater-like lesion in a membrane; ulcers that develop in areas of the gastrointestinal tract are called peptic ulcers [1]. Peptic ulcer is one of the most common diseases in present day society. An ulcer consists of two major structures; a distinct ulcer margin formed by the adjacent non-necrotic mucosa - the epithelial component, and granulation tissue at the ulcer base, which consists of fibroblasts, macrophages and proliferating endothelial cells forming microvessels [2]. Gastric and duodenal ulcers may result when *Helicobacter pylori* weakens the protective mucous coating of the stomach and duodenum, allowing acid to get through to the sensitive lining beneath. Gastric hydrochloric acid and *Helicobacter pylori* can irritate the lining and

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cause an ulcer to form. Long term use of non-steroidal anti-inflammatory drugs such as aspirin (an anti-platelet), ibuprofen and naproxen (non-steroidal anti-inflammatory drugs) can also cause ulcer. Ulcer treatment involves the use of drugs that eradicate the stomach population of *Helicobacter pylori* and also reduce the gastric acid production [3]. Peptic ulcer is due to exposure of stomach and duodenum to pepsin, gastric acid and ulcerogen. Imbalance occurs between aggressive factors like acids, pepsin, *Helicobacter pylori*, and defensive factors such as gastric mucus, bicarbonate ions and prostaglandins along with innate resistance of mucosal cells [4]. Gastro-duodenal mucosa utilizes several defense mechanisms against the aggressive factors such as hydrochloric acid and pepsin [5].

Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). It is shown to bind directly to the reverse transcriptase of HIV-1 and blocks polymerase activity by causing disruption of the enzyme's catalytic site [6]. The study of the effect of antiretroviral drugs on the gastrointestinal tract is of paramount importance. Gastrointestinal (GI) disorders which are among the most common features of HIV are largely a result of opportunistic infections [7, 8]. Advent of highly active antiretroviral therapy (HAART) in 1995 has decreased the incidence of serious opportunistic infections in the gastrointestinal system as well as other sites, [8]. Despite this, GI abnormalities are common among HIV infected patients [9-11].

Hence, the present study was designed to examine the therapeutic potential of nevirapine in gastric lesions induced by ethanol and pyloric ligation, and its ulcer healing activities in acetic acid-induced chronic ulcer model in Wistar rats.

Materials and method

Animals

One hundred and thirty-five female Wistar rats (120-150g) were obtained from the Central Animal House, College of Medicine, University of Ibadan, Nigeria. Each group of the acute models consisted of six rats while each group of the chronic model consisted of nine rats. The animals were housed in a raised mesh bottom metal cages to prevent coprophagy and kept in environmentally controlled rooms (25 ± 2°C, 12hours light and dark cycle). They were maintained under standard laboratory conditions and the animals were fed with standard rat pellet (Ladokun Feeds, Nigeria) and water *ad libitum*. All procedures in this study conformed to the guiding principles for research involving animals as recommended by the Declaration of Helsinki and National Institute of Health [12], and as approved by the Physiology Research Ethical Committee, University of Ibadan, Nigeria.

Drugs and Chemicals

Nevirapine (Boehringer Ingelheim, Germany), omeprazole (Swiss Pharma, India), ketamine hydrochloride (Rotexmedica), and xylazine (V.M.D, Belgium) were used for the study. Acetic acid: A stock concentration of 100% Acetic acid was diluted with distilled water to 40% v/v in a conical flask and mixed thoroughly before use for the induction of ulcer.

Evaluation of anti-ulcer studies

Cold restraint stress-induced (CRU) gastric ulcer model in rats

The rats were subjected to cold-stress paradigm [13] after 45 min of treatment of nevirapine (9, 18, 36 mg/kg, p.o.) and omeprazole (10 mg/kg, p.o.). All the animals were immobilized in a restraint cages, kept at 4°C in an environmental chamber for 2 hours and then sacrificed thereafter. The stomach was cut along the lesser curvature and ulcers were scored with the help of magnascope.

Ethanol-induced gastric ulcer model in rats

The rats were pre-treated with graded doses of nevirapine (9, 18, 36 mg/kg). Control received vehicle only and standard group was pre-treated with ranitidine (20 mg/kg), through oral gavage daily for 7 days, and then fasted for 24 hours. On the 8th day, after fasting for 24 hours, the animals were pre-treated with either graded doses of nevirapine, vehicle or ranitidine, 1 hr before oral administration of 1ml/200g of cold absolute alcohol. One hour later, the animals were anaesthetized with ether and the stomachs were removed to determine the gastric lesion index [14].

Gastric lesion index

The stomach were removed, opened along the greater curvature and fixed in shapes to determine gastric lesion index. Ulcer index was calculated using severity scores and average number of ulcers per animal [15].

Criteria for scoring

0 - Normal stomach; 0.5 - Red coloration; 1 - Spot ulcers; 1.5 - Haemorrhagic streaks; 2 - Ulcer > 3 mm but <5 mm; 3 - Ulcers > 5 mm

Calculation of ulcer Index

$UI = (U_S + U_P) \times 10^{-1}$

(where UI = Ulcer Index; U_S = Average severity of ulcer score, U_P = Percentage of animal with ulcer incidence).

Percentage inhibition was calculated by the formula

Percentage protection =

$$\frac{\text{(Control mean ulcer index – Test mean ulcer index)} \times 100}{\text{Control mean ulcer index}}$$

The size of the gastric lesions was measured and compared to the control group. The observer of gastric lesions was blind to the treatments.

Pyloric ligation-induced ulcer in rats

Animals were pre-treated with graded doses of nevirapine (9, 18, 36mg/kg). Control received vehicle only and standard group was pre-treated with ranitidine (20mg/kg), through oral gavage for 7 days and then fasted for 24 hours. On the 8th day after fasting for 24 hours, they were given nevirapine again. Then, 30minutes later, each rat was anaesthetized with ether, the abdomen was opened, and the pylorus was ligated. The rats were allowed to recover and stabilize in individual cage during post-operative period. After 4hours of surgery, the rats were humanely sacrificed and gastric juice was collected for performing gastric secretory study. Ulcer scoring was done on stomach [16].

Evaluation of ulcer-healing activity

Acetic acid-induced ulcer model in rats

Ulcers were induced by local application of acetic acid to mucosal surface of the stomach as described earlier [17]. The animals were anaesthetized with xylazine and ketamine (short time anesthesia) through intraperitoneal administration. Midline incision was made and stomach was taken out. Serosal surface of glandular portion of stomach was exposed to 0.06ml of 40% acetic acid for 45secs [18]. The serosa was cleaned with normal saline and then returned to its original position in the abdominal cavity. The abdominal wall was closed in layers. The external surface of the suturing was then dressed with procaine penicillin so as to prevent bacterial infection. The animals were allowed to recover fully. Omeprazole and nevirapine therapy started on 3rd day of surgery and lasted for 15 days. Five rats of each group were sacrificed by decapitation on days 3, 7 and 14 of therapy. The stomachs were excised and fixed by injection of 5ml of 10% formalin. After 5 minutes, stomach was cut open along the greater curvature. The longitudinal and abscissal length of ulcer base was measured and area (mm^2) was calculated, which is taken as a measure of ulcer index. Stomach was again immersed in formalin for 24 h. Paraffin blocks were made by embedding tissue for 4 h in an automatic block making machine. A section of 5 micrometers was made with the help of automated microtome. Haematoxylin and eosin staining (H&E) was done and stained slides were visualized with stereomicroscope with magnifications of X 40, X100 and X200 and photomicrographs were taken for respective slides.

Statistical analysis

All values are expressed as mean ± S.E.M. The ulcer index data were analyzed by non-parametric ANOVA followed by Newman-Keul's multiple comparison test and other data was evaluated by one-way ANOVA followed by Newman-Keul's multiple comparison test using Graph Pad PRISM software. $P<0.05$ was considered significant.

Results

Anti-ulcreogenic activities of nevirapine in cold restraint stress-induced gastric ulcer

As shown in figure 1, nevirapine significantly reduced ulceration at doses of 9mg/kg by 35.7% ($p<0.05$); 18mg/kg by 68.6% ($p<0.01$); and 36mg/kg by 67.2% ($p<0.01$) when compared with the control group. Omeprazole (10mg/kg) also significantly reduced the ulcer formation by 84.2% ($p<0.01$) when compared with the control group

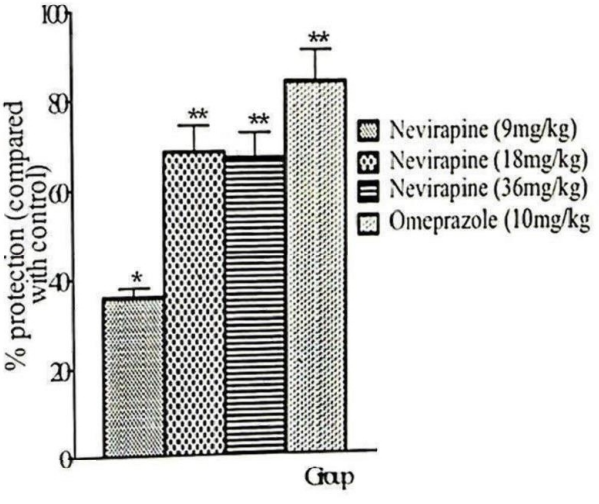

Fig. 1: Effects of nevirapine and omeprazole on the mean ulcer severity score in cold restraint stress-induced gastric ulcer. Data represent means ± S.E.M of 6 rats, *p<0.05; **p<0.01.

Anti-ulcreogenic activities of nevirapine in ethanol-induced gastric ulcer

Nevirapine significantly reduced ulceration at doses 18mg/kg (2.13±0.77) and 36mg/kg (1.25±0.75) when compared to control ($P<0.001$). Ranitidine also significantly reduced ($P<0.001$) ulceration at dose 20mg/kg (4.0±0.43) when compared with the control (9.30±1.32) as shown in figure 2.

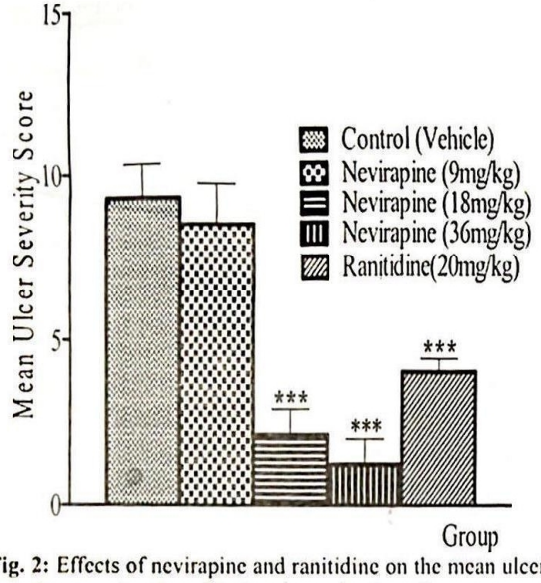

Fig. 2: Effects of nevirapine and ranitidine on the mean ulcer severity score in ethanol-induced gastric ulcer. Data represent means ± S.E.M of 6 rats. ***p<0.001.

Anti-ulcerogenic activities of nevirapine in pyloric ligation-induced gastric ulcer

In the pyloric ligation model of gastric ulcer, ulcer sore was significantly reduced (P<0.001) by graded doses of nevirapine 9mg/kg (7.0±0.58), 18mg/kg (2.4±0.80) and 36mg/kg (1.25±0.75), and ranitidine (0.8±0.60) when compared to the control (12.0±1.32) as shown in figure 3.

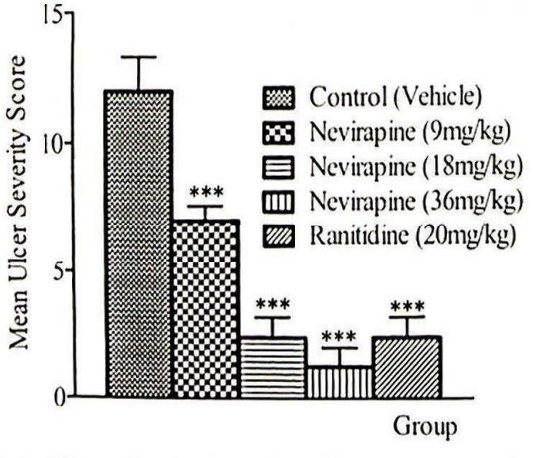

Fig.3: Effects of nevirapine and ranitidine on the mean ulcer severity score in pyloric ligation induced gastric ulcer. Data represent means ± S.E.M of 6 rats. ***p<0.001.

Effect of nevirapine on the pH of gastric juice in pyloric ligation-induced gastric ulcer.

As shown in figure 4, there was no significant increase in gastric juice pH of the doses except from the group treated with 36mg/kg (1.50±0.16) dose of nevirapine (*p<0.05), when compared with the control (0.8±0.04).

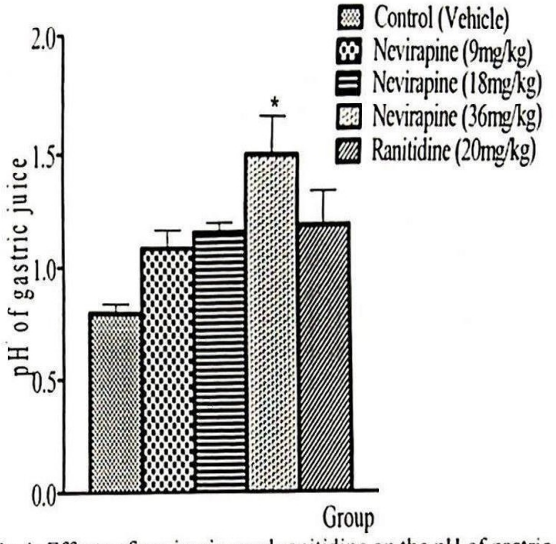

Fig.4: Effects of nevirapine and ranitidine on the pH of gastric juice in pyloric ligation-induced gastric ulcer. Data represent means ± S.E.M of 6 rats. *p<0.051.

Ulcer-healing effect of nevirapine

As shown in plate 1, the administration of nevirapine (18mg/kg and 36mg/kg) on the acetic acid-induced ulcer in rats showed significant ulcer healing after 3, 10 and 14days of treatments. Moreover, complete healing of ulcer was observed after 14days of treatment with nevirapine (36mg/kg).

Histopathology of the gastric mucosa in acetic acid-induced ulcers

On day 3 of ulcer induction, rats showed extensive chronic ulcer with acute necrotic mucosa in the stomach. The mucosa surface epithelia were eroded with moderate to severe haemorrhage, moderate infiltration of inflammatory cells within the mucosa layer, and the submucosa was severely infiltrated with mild oedema.

Throughout the duration of the experiment, the stomach of the control animals showed normal histology. In animals treated with nevirapine (9 and 18mg/kg), there was mild mucosal and submucosal infiltration by inflammatory cells. The circular muscle appeared normal. The mucosa and submucosa of the 36mg/Kg nevirapine group appeared normal with no cellular infitration. In the ulcer induced group that received no treatment, dilated vessels with severe vascular congestion were

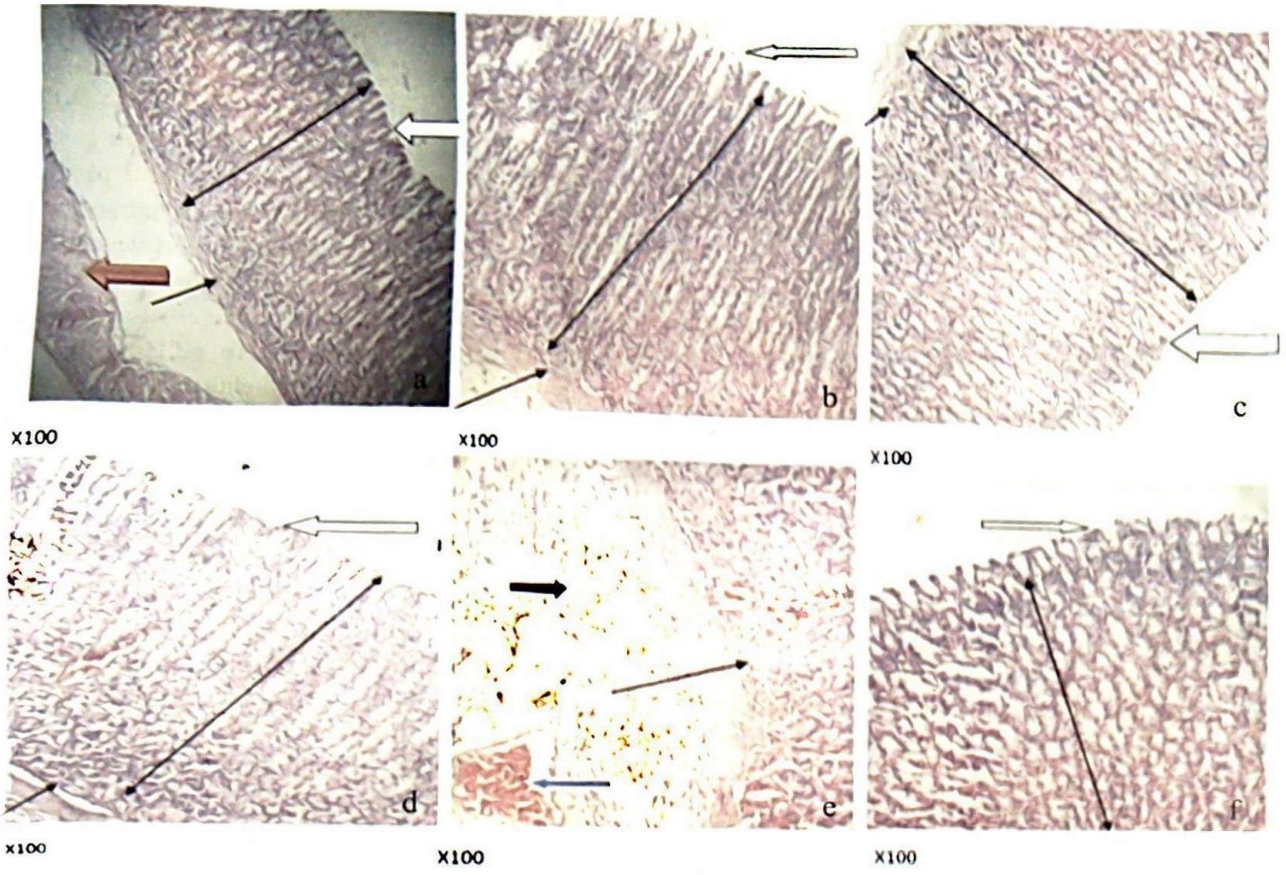

Plate 1: Sections of stomachs obtained from rats of (a) control; white arrow (the mucosa surface epithelia not eroded), slender arrow (no infiltration of inflammatory cells within the submucosa), spanned arrow (mucosa layer), red arrow (the circular muscle). (b) 9mg/kg nevirapine; white arrow (mucosa surface epithelia appear poorly preserved), slender arrow (scanty infiltration of inflammatory cells within the submucosa), spanned arrow (mucosa layer). (c) 18mg/kg nevirapine; white arrow (the mucosa surface epithelia appearing normal), spanned arrow (there is no infiltration of inflammatory cells within the mucosa layer and its lamina propria), slender arrow (the submucosa) appear normal and is not infiltrated and vessel seen without congestion. (d) 36mg/kg nevirapine; white arrow (the mucosa surface epithelia appearing normal with no erosion), spanned arrow (there is no infiltration of inflammatory cells within the mucosa layer and its lamina propria), slender arrow (the submucosa appears normal and is not infiltrated). (e) Ulcer induced with no treatment; black arrow (severe focal area of edema below the submucosa layer), slender arrow (acutely inflamed by polymorphonuclear cells, lymphocytes and plasma cells), spanned arrow (there is mild infiltration of inflammatory cells within the mucosa layer), blue arrow (mildly congested vessels). (f) 10mg/kg Omeprazole white arrow (mild papillary infolding and moderately preserved mucosa surface epithelia), spanned arrow (moderate infiltration of inflammatory cells within the mucosa layer), slender arrow (the submucosa layer), in acetic acid-induced ulcer model in rats after 14 days of treatment (n=6 in each group). HE 100X.

seen. There was severe inflammation of the gastric mucosa with extensive submucosa infiltration. Also, the submucosal was noted to be oedematous in the omeprazole group. Focal areas with moderate ulcer were seen with moderate infiltration of the mucosa and submucosa by inflammatory cells.

Day 10 post induction (day 7 of therapeutic intervention), the 9 mg/kg and 18 mg/kg nevirapine groups very mild infiltration of the mucosa and submucosa by inflammatory cells with neutrophils predominating. No ulcer was seen.. The nevirapine (36mg/kg)-treated group showed normal mucosa with non congested vessels. However, the untreated group showed severe oedema of the area below the submucosa layer. The submucosa was severely infiltrated. The omeprazole group showed mild infiltration of the mucosa and submucosa with erosion of the epithelium.

After 14 days of treatment (day 17 of ulcer induction), the rats in the nevirapine-treated (9mg/kg and 18mg/kg) groups (Plates 4b and 4c), showed neither vascular congestion nor visible ulcer. In the group treated with 36mg/kg of nevirapine (Plate 4d), the mucosa surface epithelia appeared normal with no erosion of the mucosa layer. However, in the control (Plate 4e), severe focal area of oedema was seen below the submucosa layer which is acutely inflamed by polymorphonuclear cells, lymphocytes and plasma cells with mild congested vessels. Omeprazole-treated group (Plate 4f) showed mild

papillary infolding and moderately preserved mucosa surface epithelia.

Discussion and Conclusion

Nevirapine has been used effectively as an antiretroviral drug, and has been reported to cause a decrease in the incidence of gastrointestinal manifestations of HIV-AIDS like diarrhoea, vomiting, oesophagitis, malabsorption and nausea [19] but adverse effects like rashes and hepatitis are common [20,21].

The present study reported the antiulcer effects of the antiretroviral drug, nevirapine, on cold restraint stress-induced gastric ulcer, ethanol-induced gastric ulcer, pyloric ligation-induced ulcer and acetic acid-induced chronic ulcer models in rats. Although, the aetiology of ulcer is not well known, there are several factors that may induce ulcers such as stress, chronic alcoholism and frequent use of non-steroidal anti-inflammatory drugs (NSAIDs). In general, it can be perceived that, ulcer is the result of an imbalance between aggressive factors and defensive factors, that maintains the mucosa integrity through the endogenous defense mechanism [22].

Cold restraint stress-induced (CRU) gastric ulcer model has been suggested to be a well acceptable model of gastric ulcer induction. It is considered to be a model for screening potential antiulcer drugs and its selection was premised on the findings of previous studies [23]. It suggests that peripheral sympathetic activation plays an important role in induction of ulcers by restraint. Vagal over-activity has been suggested to be the principal factor in stress-induced ulceration [24]. This simply means stress-induced ulcer can be prevented partially or entirely by vagotomy. Also, in CRU, incidence of ulcers is due to increased acid secretion and generation of free radicals, amongst other factors. Nevirapine significantly decreased the ulcer index in this model when compared to control. So, nevirapine may be involved in the negative influence on the vagal activity. Also, it might have mediated its antiulcer property through inhibition of acid secretion.

It has been proposed that in pyloric ligation, the digestive effect of accumulated gastric juice and interference of gastric blood circulation are responsible for induction of ulceration [25]. In pyloric ligation, ulcers develop due to accumulation of gastric acid and pepsin which may lead to auto-digestion of gastric mucosa [26].

Ethanol-induced gastric lesion formation may be due to stasis in gastric blood flow which contributes to the development of the haemorrhage and necrotic aspects of tissue injury [27]. Ethanol-induced ulcers are due to direct necrotizing effect of ethanol on gastric mucosa ([28] and causes necrosis of superficial epithelial cells on gastric mucosa and its erosion [29]. Alcohol rapidly penetrates the gastric mucosa apparently causing cell and plasma membrane damage leading to increased intracellular membrane permeability to sodium and water. The massive intracellular accumulation of calcium represents a major step in the pathogenesis of gastric mucosal injury. This leads to cell death and exfoliation in the surface epithelium [30].

The results of ethanol-induced ulcer model showed reduction in the incidence of ulceration in the rats treated with varying doses of nevirapine when compared to the control group. Also, there was a significant reduction in the incidence of ulceration in rats pre-treated with ranitidine, when compared to the rats in the control group. Nearly, all the rats in the control group had haemorrhagic streak while some had ulcers. Then, subsequently, in other groups pre-treated with different doses of Nevirapine and the standard drug, the number of haemorrhagic streaks reduced. The mean ulcer severity score of the animals used in this model was observed to decrease as the dosage of nevirapine increased. Percentage inhibition of ulceration compared to the control group (77%; 94%; 96%, and 89% for groups treated with 9mg/kg, 18mg/kg, 36mg/kg dose of nevirapine and ranitidine respectively) shows that nevirapine possesses gastric protective proprties in a dose dependent manner. It could be explained as well that nevirapine probably might have reduced or partly prevented the direct necrotizing effect of ethanol on gastric mucosa [28], which could have been responsible for the necrosis and erosion of superficial epithelial cells on gastric mucosa. Also, nevirapine might have strengthened the integrity of the mucous layer of the stomach, although, more confirmatory experiments may be needed to give such confirmatory statement.

In the pyloric ligation model, it was observed from the animals in this model that all the rats in the control group had haemorrhagic streak while some had ulcers. However, in the pre-treated groups (nevirapine and standard drug), reduced haemorrhage was noted. The proportionate ulcer inhibition of nevirapine (71%- 9 mg/kg; 80%- 18mg/kg; and 89%- 36mg/kg) and ranitidine (80%) could infer dose dependent gastroprotective ability of nevirapine.

Acetic acid-induced ulcer model in rats has been demonstrated to be similar to human ulcers [17]. In this acetic acid-induced chronic ulcer model

experiment, the use of different doses of nevirapine on acetic acid-induced chronic ulcer produced significant effect in the healing of ulcer. This effect was found to be dose-dependent. From previous studies, it was established that antisecretory drugs such as cimetidine and omeprazole could markedly accelerate gastric ulcer healing in rats [31,32]. The disappearance of ulcer in the nevirapine groups as early as 3rd of therapy could connote its anti ulcer property. Also, it was noted that nevirapine possessed more ulcer healing potential than omeprazole. The group induced with ulcer but with no treatment produced the expected characteristic microscopic appearance of ulcer including inflammatory exudates, infiltration by inflammatory cells. After 7 days of treatment, results further accentuated the difference between the healing properties of nevirapine and omeprazole, as nevirapine appears to be more active than omeprazole in ulcer healing.

After 14 days treatment with nevirapine (18mg/kg and 36mg/kg) microscopic appearance of ulcer could not be detected. Nevirapine at 9mg/kg was shown to have scanty infiltration of inflammatory cells and the mucosa was observed to be poorly preserved. The omeprazole group had mild inflammatory cellular infiltration with mild papillary epithelial infolding due to hyperplasia [33].

Regeneration of mucosa glandular structure as observed may be due to nevirapine cytoprotective activity coupled with anti-secretory effect. The acceleration in the healing of the ulcer base might be due to protection of basic fibroblast growth factors (bFGF) from acid. Basic fibroblast growth factor is considered to be responsible for epithelial regeneration in acid induced ulcers [34]. Anti-secretory agents like omeprazole [35] have been found to be effective in acetic acid model. Their efficacy has been attributed to their anti-secretory and cytoprotective effect. The proton pump inhibitors like omeprazole, is the most effective antisecretory agents available for treatment of gastric acid related diseases [36]. Ulcer healing involves cell migration, proliferation, re-epithelialization, angiogenesis and matrix deposition. Mucosa of ulcer margin forms a healing zone. The epithelial cells lining glands of the ulcer margin express epidermal growth factor receptor (EGF-R) and actively proliferate. These cells migrate from the ulcer margin onto the granulation tissue to re-epithelialize the ulcer base [37]. Ulcer-healing depends on regeneration of mucosa glandular structure and migration of epithelial cells to cover ulcer crater [34]. Omeprazole aids in ulcer healing by their gastric acid inhibitory action and also the up-regulation of cyclooxygenase-2 in the ulcer area. Repair is by hyperplasia of gastric glands at the ulcer margins [33]. Hence, nevirapine may have gastric acid inhibitory action as well as a stimulatory effect on the ulcer healing process.

In conclusion, it can be suggested that nevirapine may have anti-ulcer potential and that the ulcer healing potential of nevirapine may be dose dependent in the cold restrained stress-induced, ethanol-induced, pyloric ligation-induced and acetic acid-induced ulcer models in rats. The pH of gastric juice also increased with increased dosage of nevirapine, showing reduction in acidity. These show that the gastric ulcer healing properties of nevirapine and the rate at which it heals ulcer makes the drug a plausible candidate for further *in vivo* studies. This may be a good report for HIV-AIDS patients with gastrointestinal complications. Further studies on the mechanisms of the gastroprotective effect of nevirapine remain to be established.

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