Dyspepsia in Nonsteroidal Anti-inflammatory Drugs Gastropathy

Chudahman Manan, Bambang Pontjo Priosoeryanto**, Daldiyono*, Sri Estuningsih**, Min Rahminiwati****

* Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta
**Department of Veterinary Clinic, Reproduction and Pathology, Faculty of Veterinary, Bogor Agricultural University, Bogor
***Department of Anatomy, Physiology and Pharmacology Faculty of Veterinary, Bogor Agricultural University, Bogor

ABSTRACT

Background: *Nonsteroidal anti-inflammatory drugs (NSAIDs) gastropathy is a common complication, which has characteristic symptoms of dyspepsia syndrome. Mostly, it includes epigastric discomfort with bloating and nausea. The aim of this study was to provide evidences that clinical symptoms of dyspepsia are related to macroscopic changes of gastric form in rats, which are expected to be applied in human.*

Method: *The study was conducted in 20 white rats (Rattus norvegicus, Sprague-Dawley strain) at the Department of Pathology and Clinical Reproduction, Bogor Agricultural University between January and December 2008. The rats were divided to treatment group and control group and each group consisted of 10 rats. Acetyl salicylic acid (ASA/aspirin) was administered at 400 mg dose, diluted in distilled water and was given to the treatment group using gastric cannula, once daily for three days period; while the control group had received aquabidest only. Subsequently, necropsies were conducted for both groups, followed by macroscopic observation and measurement of sagittal and transversal diameter. Gastric incisions along the minor curvature were performed in both groups to recognize any macroscopic changes of gastric mucosa. ANOVA test was utilized for data analysis, which was followed by Duncan test when the results were significant.*

Results: *Gastric diameters in treatment group with positive lesion were significantly different from the control group and the treatment group with negative lesion on anthrum/pylorus region, with $p < 0.05$.*

Conclusion: *Prominent gastric dilatation at anthrum/pylorus region found in the treatment group may become the initial cause and signs of dyspepsia in human.*

Keywords: *NSAID gastropathy, dyspepsia, NSAIDs/aspirin, gastric dilatation*

ABSTRAK

Latar belakang: *Obat anti-inflamasi non steroid (OAINs) gastropati merupakan komplikasi yang sering ditemukan, yang mempunyai karakteristik gejala sindroma dispepsia dengan keluhan perasaan tidak nyaman di daerah epigastrium disertai kembung dan mual. Tujuan penelitian ini yaitu untuk membuktikan gejala klinis dispepsia terhadap perubahan pengamatan makroskopik pada lambung tikus diharapkan dapat mencerminkan pada manusia.*

Metode: *Penelitian ini dilakukan pada 20 ekor tikus putih Rattus norvegicus jenis Sprague-Dawley di Bagian Patologi dan Klinik Reproduksi, Institut Pertanian Bogor dari bulan Januari sampai Desember 2008. Tikus tersebut dibagi dalam dua kelompok; kelompok kontrol dan terapi. Aspirin yang dilarutkan air suling dengan dosis 400 mg diberikan pada kelompok terapi dengan kanul lambung, sekali sehari selama 3 hari. Sedangkan pada kelompok kontrol diberikan air suling saja. Sesudah itu dilakukan nekropsi terhadap kedua kelompok dan dilakukan pengamatan makroskopik lambung, serta dilanjutkan pengukuran diameter sagittal dan transversal.*

Untuk mengetahui perubahan makroskopik mukosa lambung dilakukan insisi sepanjang kurvatura minor pada kedua kelompok. Analisis data dilakukan dengan tes ANOVA dan dilanjutkan dengan tes Duncan untuk hasil yang bermakna.

***Hasil:** Diameter kelompok dengan terapi aspirin dengan lesi mukosa positif mempunyai perbedaan bermakna dengan kelompok kontrol, dan kelompok terapi aspirin lesi mukosa negatif pada regio antrum/pilorus, dengan nilai $p < 0.05$.*

***Kesimpulan:** Dilatasi gaster dari kelompok tikus yang mendapat aspirin dengan lesi mukosa gaster regio antrum dapat menjadi model untuk melihat munculnya gejala dan tanda dispepsia pada manusia.*

***Kata kunci:** OAINs gastropati, dispepsia, NSAIDs/aspirin, dilatasi gaster*

INTRODUCTION

Aspirin has been widely used for many clinical entities such as rheumatic diseases, heart diseases, stroke, and hematologic disorders. With a wide spectrum of indication, the use of aspirin is usually associated with gastrointestinal complication, especially on the stomach. The initial symptoms of such complication may appear syndrome of dyspepsia.[1-5] Complications may occur in mild to severe form including gastric ulcer either with or without bleeding. In some cases, a more serious complication such as perforation probably present.[5-7] In human, mostly it is difficult to determine the etiology of dyspepsia since we could not detect any macroscopic changes of the stomach directly. In animal experimental study, such problem could be solved since we could easily perform necropsy or tissue resection after the animal had been treated with aspirin. The necropsy would reveal the whole contour of stomach and mucosal lesion. Some studies have indicated that clinical symptoms are not directly associated with gastric mucosal abnormalities; however, the occurrence of gastric complication may be recognized through observation of clinical symptoms, including the dyspepsia syndrome.[5,6,8]

The hypothesis of this study was that aspirin would induce gastric mucosal lesions with initial sign of gastric dilatation, which may be related to dyspepsia symptoms. The most common symptoms are epigastric discomfort or epigastric pain, bloating, nausea and vomiting. If those symptoms persist, usually other symptoms may occur such as melena with or without hematemesis. Dyspepsia is initial symptom of nonsteroidal anti-inflammatory drug (NSAID) gastropathy, which may be related to gastric functions. The etiology of dyspepsia due to gastric dilatation may be associated with mucosal inflammation of anthrum. Gastric mucosal lesions caused by NSAID mostly occur as a result of direct contact between the drug and mucosa because of impaired mucus secretion. The condition is associated with the type of drugs, duration of drug contact to the mucosa, and the role of pH in gastric lumen. The durability of gastric mucosa is correlated with pre-epithelial, epithelial and sub-epithelial component.[8,9] The aim of this study was to provide evidences that clinical symptoms of dyspepsia are related to macroscopic changes of gastric form in rats which are expected to be applied in human.

METHOD

The animals used for this study work were 20 male white rats (*Rattus norvegicus)* of Sprague-Dawley strain. The rats were 2 months old and the average weight of each rat was ± 250 g. The animals obtained from the Department of Animal Production, Non Ruminant and Prospective Animal Division, Faculty of Animal Sciences, Bogor Agriculture University. The study was conducted at Department of Pathology and Clinical Reproduction, Faculty of Veterinary Science, Bogor Agricultural University, between January and December 2008. The animals were categorized into two groups, i.e. the control group and treatment group. Each group consisted of 10 rats.

Acetyl salicylic acid (ASA/aspirin) at 400 mg dose diluted in distilled water was administered to the treatment group; while the control group was given distilled water only. Preliminary study, including adaptation and pre-treatment study had been conducted to minimize bias and to adjust factors that may affect gastric mucosa. Each rat was kept separately in a modified cage and the rats were fed ad libitum. The food was provided as pellet that had been treated with irradiation of 10 kGray to ensure sterility. In the three-week preliminary study, the rats were administered a dose of 250 mg/kgBW of tetracycline for three days and a single dose of albendazole 5%, an antihelminthic agent, once in a week. Subsequently, they were also given a dose of 50 mg/kgBW of fluconazole, an anti-*cryptococcus*, once daily for three

days. The weight of those rats and food pellet residue were calculated every day. ASA was administered orally to the rats in treatment group by using gastric cannula. Prior to ASA administration, the rats were having three-hour fasting, which subsequently followed by administration of 400 mg ASA dissolved in 2 ml distilled water once daily for three days.

Afterwards, rats were sacrificed by performing necropsy in both groups using ether for anesthetic. Necropsy was initiated along the alba line by opening skin layer and fascia. The stomach was separated from its surrounding tissue and finally was detached. Before performing stomach incision, the sagittal and transversal diameters of stomach were measured.

Quantitative data were analyzed using one-way ANOVA test and SPSS software version 13.0. ANOVA was utilized to compare control (C) group, treatment group with negative lesion (TNL) and treatment group with positive lesion (TPL). When the results were significant, it was followed by Duncan test, with p value of < 0.05.

RESULTS

The results of this study included measurement of sagittal and transversal gastric diameter (Table 1 and 2) between C group, TNL group and TPL group, and macroscopic observation of gastric fundus/corpus (Figure 1 and 2).

Table 1. Differences of diameter measurement between C, TNL, and TPL group on the fundus/corpus region

Diameter length	Fundus/corpus			
	C	TNL	TPL	p
Sagittal	9.33+0.51	9.86+1.76	9.75+0.92	> 0.05
Transversal	4.29+0.28	4.77+0.92	4.40+0.14	> 0.05

*C: control; TNL: treated negative lesion; TPL: treated positive lesion

Statistically, there was significant difference of gastric sagittal and transversal diameter between TPL and C or TNL group. However, no significant difference was found regarding sagittal and transversal diameter between TNL and C group (Table 2).

Table 2. Differences of diameter measurement between C, TNL, and TPL group on the antrum/pylorus region

Diameter length	Antrum/pylorus		
	C	TNL	TPL
Sagittal	9.33 ± 0.51^a	8.75 ± 1.29^a	10.70 ± 1.22^b
Transversal	4.29 ± 0.28^a	4.28 ± 0.29^a	5.20 ± 1.02^b

* C: control; TNL: treated negative lesion; TPL: treated positive lesion; *the different alphabet shows $p < 0.05$

The contour of the rat stomach in treatment group was found to have gastric dilatation, both in sagittal and transversal diameter, especially in anthrum/pylorus region.

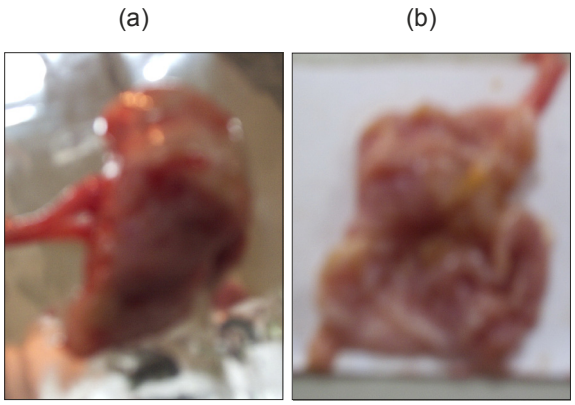

Figure 1. Macroscopic abnormalities of whole stomach part (a) and incised part of stomach (b) with dilatation

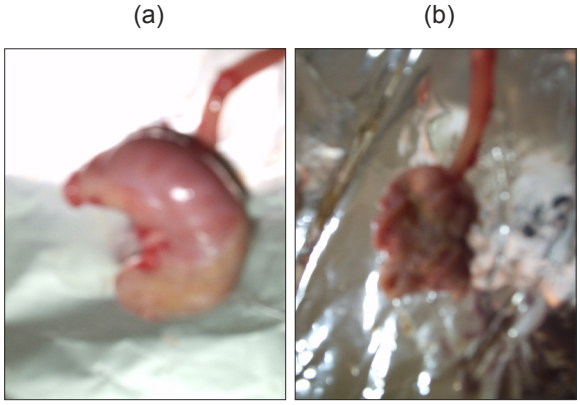

Figure 2. Normal macroscopic appearance of whole stomach part (a) and incised part of stomach (b)

DISCUSSION

This study would explain more thoroughly about the length of contact between aspirin and gastric mucosal. The length of the contact time depend on the gastric mucosal condition. The initial process of gastric lesion due to inflammation, continued by discharge of inflammatory mediators result to edematous mucosa. This condition will be occured delayed gastric emptying. Mucosal lesion occur more faster, due to prolong time contact between the drug and the mucosal. Inflammatory cell, which is one of defensive factors, will increase on the mucosal layer that will be infiltrated the layer, especially on muscularis mucosa area, followed by its surrounding tissue edema, therefore gastric motility will be decreased. This condition can affect the gastric shape due to gastric emptying disorder. If these symptoms persist, gastric dilatation is likely to occur. This condition related to clinical symptoms, likely motility disturbances. Gastric dysmotility will be influenced gastric emptying. The occurrence of mucosal lesion due to aspirin is determined by the pre-epithelial

condition, especially the mucus function as the fore mucosal barrier.[7,8,10]

Previous studies show that the occurrence of gastrointestinal side effect caused by NSAIDs is usually based on clinical symptoms. The most common side effect is dyspepsia syndrome. Epigastric discomfort with or without pain, bloating, nausea and vomiting are common symptoms of gastric disorder.[1-5]

This study was aimed to reveal the pathophysiology of dyspepsia, which has not been done before since the contour of human stomach could not be seen clearly. This study has been performed in white rats, an animal experimental study, which the results are expected to be applied in human.

This study has revealed altered gastric contour in treatment group with mucosal lesion. Such changes may be associated with infiltration of inflammatory cells, especially the mucosal neutrophils which have reached epithelial cells. Inflammatory cells in the muscularis mucosa layer and tissue edema may affect stomach motility.[5,6,7] Furthermore, it may cause impaired gastric clearance and gastric emptying leading to accumulation of gastric content, including aspirin. The risk is greater when there is longer duration of contact between the drug and gastric mucosa, which may induce the development of mucosal lesion. This study showed that there was increased length of sagittal and transversal diameter in the treatment group with mucosal lesion. Although gastric dilatation was observed on the mucosal lesion of corpus/pylorus, but there was no significant difference of gastric diameter between the treatment group without lesion and the control group. It could be explained since mucosal lesion on anthrum/pylorus region are more frequently found than corpus/pylorus region; therefore, it may be associated with the clearance of anthrum region and the duration of aspirin exposure on gastric mucosa.[7,11]

CONCLUSION

Dyspepsia syndrome is a collection of initial symptoms that may reveal the occurrence of gastrointestinal complication associated with NSAIDs. The syndrome may be caused by gastric dilatation and as result of motility disorder, which may delay clearance of gastric contents from antrum to duodenum. The occurrence of mucosal lesion is affected by the length of aspirin exposure on gastric mucosa. Prominent gastric dilatation at anthrum/pylorus region found in the treatment group of this study may become the initial cause and signs of dyspepsia in human.

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Correspondence:
Chudahman Manan
Division of Gastroenterology, Department of Internal Medicine
Dr. Cipto Mangunkusumo General National Hospital
Jl. Diponegoro No. 71 Jakarta 10430 Indonesia
Phone: +62-21-3153957 Facsimile: +62-21-3142454
E-mail: chudahmanm@yahoo.com