

THE ULCEROGENIC EFFECT OF INDOMETHACIN IN DIABETIC RATS

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Abstract - We have studied the ulcerogenic effect of indomethacin in streptozocin - induced diabetic rats. Streptozocin (65 mg kg^{-1}) was injected intraperitoneally to male Wistar rats. The blood glucose concentration was determined continuously. Blood glucose level increased significantly ($P < 0.001$) after 30 days. Gastric erosions were induced by intraperitoneal injection of indomethacin (50 mg kg^{-1}) in fasted animals. A significant ($P < 0.001$) increase in ulcer index was found in diabetic rats.

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INTRODUCTION

It is reported that gastric dysfunction is more common in diabetic patients than in the general population (1). The complications of ulcer are more frequent and more severe in diabetic patients (2). Gastric erosions and/or ulcers were observed in 32.1% of the diabetic rats and 9.7% of the non-diabetic siblings. Differences in the frequencies of lesions in two groups were significant (3). Acid back-diffusion plays an important role in the formation of mucosal haemorrhagic ulcer in diabetic rats (4).

The possible effect of aspirin - like drugs on gastric mucosal blood flow are therefore complex with both direct effects and those as consequences of acid back - diffusion. The observed actions could well depend on the dose and route of administration. Furthermore, any hyperaemic response to acid back-diffusion caused by these aspirin - like drugs may be attenuated by their concurrent direct effects on the microvasculature. Thus, the potency of non-steroidal anti-inflammatory agents in causing either or both actions may give a good indication of the ability of such drugs to cause gastric erosions (5).

Streptozocin (STZ), which possesses antitumor and diabetogenic effects, is commonly used as a diabetes inducer in experimental animals (6, 7).

In this study we have investigated the ulcerogenic effect of indomethacin in STZ - induced diabetic rats. The incidence of stomach ulcer in diabetic rats was significantly more than normal rats.

MATERIALS AND METHODS

STZ (65 mg kg^{-1}) was injected to male Wistar rats intraperitoneally. From the 14th day of injection, blood glucose level was determined using the glucose oxidase method, in both control and injected groups. About 30 days after injection blood glucose level increased significantly ($P < 0.001$).

We continued our study by double injection of STZ (65 mg kg^{-1}) in twenty normal animals, with 14 day intervals.

30 days after injection, we started studying the ulcerogenic effect of indomethacin. Animals were fasted for 48h, but allowed free access to water. Rats were divided into four groups. The first group were diabetic rats and the second were normal rats; both received saline, as control groups.

Indomethacin (50 mg kg^{-1}) was injected intraperitoneally to the third and fourth groups, which were diabetic and normal animals. In all groups, animals were killed 4 hours after injection.

Before killing each animal, its blood glucose level was determined.

After killing them, the stomachs were removed, opened along the greater curvature and washed with saline. Gastric lesions were assessed macroscopically and evaluated according to their severity and scored between 0 and 4 in each stomach (8).

STZ (Upjohn) dissolved in sodium chloride injection (UPS), prepared solution contained 100 mg STZ and 22 mg of citric acid per ml. Indomethacin (Sigma) suspended in 0.9% saline at a concentration of 25 mg ml^{-1} .

The significance of differences between values was examined by Student's t-test. $P < 0.05$ was considered statistically significant. Results are

presented as mean ± s.e.m.

RESULTS

30 days after the first injection of STZ, animals considered diabetic (Fig 1).

In both control groups, no gastric lesion was observed. It was reported that lesions of gastric mucosa may be associated with direct action of STZ (9), but we

didn't find any lesion in control diabetic rats.

Indomethacin produced gastric lesions in the stomach of all the normal and diabetic rats and there was a significant increase in ulcer index of diabetic ones (Table 1).

The regurgitation of duodenal bile salts was also observed in diabetic animals.

Blood glucose level of animals which were going to be killed, was determined and a significant difference ($P < 0.001$) between two groups was seen (Table 2).

Table 1. The ulcerogenic effect of indomethacin in both normal and diabetic rats. Ulcer were induced by intraperitoneal indomethacin (50 mg kg^{-1})

	Indomethacin (mg/kg^{-1})	Grade	Mucosal Number	lesions (%)	Ulcer Index (mean ± sem)	Incidence (%)
Diabetic Rats	50	0	0	0	3.85 ± 0.76	100
		1	0	0		
		2	0	0		
		3	3	15		
		4	17	85		
Normal Rats	50	0	0	0	1.7 ± 0.48	100
		1	3	42.85		
		2	3	42.85		
		3	1	14.3		
		4	0	0		

Table 2. Differences between blood glucose level of two groups in which gastric lesions were observed

Drugs which were injected	Number of animals	Blood glucose (mg/dl) (mean ± sem)
Indomethacin (50 mg/kg^{-1})	7	75.5 ± 4.18
Indomethacin (50 mg/kg^{-1}) + STZ (65 mg/kg^{-1})	20	$180.44^* \pm 4.45$

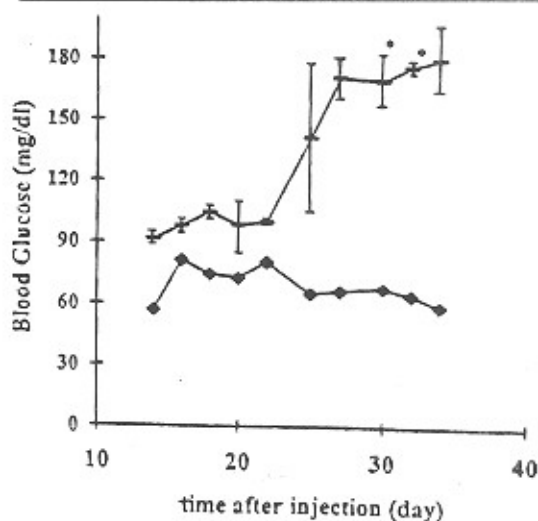


Fig. 1. The effect of STZ on blood glucose level from the 14th day of injection. Blood glucose level increased in injected animals (○) from about the 23th day of injection and it reached a definite level after about 30 days. During these days, there were no significant changes in blood glucose level in the control group (●)

* $P < 0.001$

DISCUSSION

Indomethacin - induced ulcers are generally believed to result from suppression of gastric mucus synthesis, increased free radical formation, enhancement of gastric acid secretion and inhibition of gastric prostaglandin synthesis.

The fall in gastric mucosal blood flow induced by indomethacin in doses sufficient to inhibit prostaglandin formation (10) in the mucosa (11) could suggest a role for endogenous prostaglandins (or some other product of the prostaglandin cyclo-oxygenase system) in the local regulation of the gastric microcirculation.

A previous report has demonstrated that the amount of acid back - diffusion into gastric mucosa is dependent on the concentration of free acid in the lumen (12). Also hyperglycemia which may be encountered under various conditions in diabetic patients, can result in profound enhancement of gastric acid secretion (13).

Gastric edema which is observed in the diabetic rats, due to the increase in gastric vascular permeability induced by histamine release resulting from acid back - diffusion (4).

Streptozocin - induced diabetes may produce pathological changes in the gastric mucosa, and the intraluminal acid back - diffusion into gastric mucosa through the disrupted mucosal barrier, this back-diffusion of gastric acid plays an important role in the formation of gastric haemorrhagic ulcer and edema in the diabetic rats. Also, decrease in gastric mucosal blood flow due to pathological changes in blood vessels and haemodynamics, were observed (4).

Otherwise, the reflux of bile into gastric lumen has been considered as a possible factor in the aetiology of peptic ulceration (14) and in the pathogenesis of gastric erosions induced by non-steroidal anti-inflammatory agents (15, 16).

Bile, by virtue of its surface can lead to the back - diffusion of hydrogen - ions from the lumen across the mucosa (17).

In this study we observed the regurgitation of bile salts in diabetic rats, which may due to diabetes and indomethacin administration.

It has also been reported that in normal rats hyperglycemia can prevent phenylbutazone ulcer by effect of a glycoprotein receptor system (18), however, in diabetic rats, many pathologic changes occurred in the gastric mucosa.

Following the pathological changes in gastric mucosa of diabetic rats, acid back - diffusion increases (4). Furthermore, reduction of mucosal blood flow and increase in acid back - diffusion because of indomethacin administration, and also reflux of bile salts can lead to a higher incidence of peptic ulcer in diabetic than in normal rats.

So, diabetic patients must be aware of the effects of using non - steroidal anti - inflammatory drugs, which may cause gastric complications.

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