Effects of Indomethacin on Gastric Secretion and Duodenal Ulcer Formation in Bile Duct-Ligated Rats

Diane M. Przewozniak

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EFFECTS OF INDOMETHACIN ON GASTRIC
SECRETION AND DUODENAL ULCER FORMATION
IN BILE DUCT-LIGATED RATS

by

Diane M. Przewozniak

A Thesis
Submitted to the
Faculty of The Graduate College
of the
Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
December 1977
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Diane M. Przewozniak
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INTRODUCTION

The widespread incidence of peptic gastro-duodenal ulcer represents a social and economic disease.

Duodenal ulcers are produced in rats by non-steroidal anti-inflammatory compounds (NOSAC) only when the bile duct is ligated (BDL). When indomethacin (15 mg/kg), a NOSAC, is administered orally to intact animals, severe jejunal and ileal ulcerative lesions appear within three days.4,18,25

It is believed that gastric acidity plays a role in ulcer formation. Therefore, the volume and acid content of gastric juice were determined in rats receiving indomethacin, with and without bile duct ligation. Two different techniques were used to collect gastric secretion: pylorus ligation and chronic gastric fistula.
METHODS AND MATERIALS

Gastric Secretion Studies

Female Upjohn rats weighing 190-215 gm were used. Twenty-four hours prior to experimentation, in the morning, food was removed; in the late afternoon, water was also removed. At that time, the animals were placed in cylindrical restraining cages which prevented the eating of feces so that clear, uncontaminated gastric juice could be collected. On the day of the experiment, the fasted rats were re-weighed and the appropriate concentration from the stock solution of indomethacin was calculated.

Two different techniques were used to collect gastric secretion: pylorus ligation and chronic gastric fistula.

The Pylorus Ligated Rat

Shay, et al. (1945) described the technique of pylorus ligation for the rat, in which the pyloric sphincter is tied off under ether anesthesia with 3-0 silk. Rats are killed with carbon dioxide gas, then the stomachs are dissected out and gastric juice is collected in a graduated test tube.

The general format for our studies consisted of 6 or more rats in each of the following groups: (1) Vehicle, (2) Indomethacin (15mg/kg), (3) Vehicle plus Bile Duct Ligation, and (4) Indomethacin plus Bile Duct Ligation.

In our experiments, Groups (1) and (2) were either sham operated or left intact. Sham refers to the handling of the organ (bile duct in this case) without ligating it. These two groups would then be considered
the controls for Groups (3) and (4) which did have their bile ducts ligated. The bile duct was ligated 1 cm. proximal to the duodenum. 'Intact' refers to the rats which remained surgically untouched.

One ml. of indomethacin or vehicle was administered orally two hours before pylorus ligation. Vehicle consists of carboxymethylcellulose (5 mg), polysorbate 80 (4 mg), sodium chloride (9 mg), and benzyl alcohol (9 mg).

Gastric volume, acid content, and pepsin content were then determined. The volume of gastric juice was measured to the nearest 0.1 ml. Acid content, expressed in mEq/L (concentration) and mEq/4 hr (output), was determined by titrating with 0.1 V NaOH to pH 7 with the use of a glass electrode (Copenhagen radiometer). Pepsin content was determined by the hemoglobin method (Anson, et.al., 1938) using an auto-analyzer (Vatier, et.al., 1968), and was expressed as uEq tyrosine/ml (concentration) and uEq tyrosine/4 hr (output).

The Chronic Gastric Fistula Rat

The second technique employed to collect gastric juice in the rat was the chronic gastric fistula. It consisted of implanting a stainless steel cannula in the forestomach 2-3 weeks before the time of experimentation. These rats were anesthetized with 0.5 ml of 5% sodium cycloпentenylbarbiturate (Cyclopal®) intraperitoneally. The cannula was secured to the gastric serosa by using 5-0 silk and purse-stitching around the implant, and by using a polypropylene mesh gauze (Marlex®) cut to an approximate 2.5 cm X 2.0 cm size. Marlex allowed proliferation of fibrous tissue between and over the inter-twinning spaces. The gastric cannula projects through the muscles and skin to the outside where it

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was plugged with a stainless steel machine-fitted screw. Whenever collection of gastric juice was desired, one unscrewed the plug and replaced it with a rubber tube, 7.5 cm long, designed to fit over the external portion of the cannula.

Basal secretion studies using fistulated rats were first performed in order to obtain baseline values of gastric secretion. The fistula rats were weighed and fasted in wide-wire mesh cages 24 hours prior to collection time. Volume, acid concentration, acid output, pepsin concentration and pepsin output were determined at hourly intervals for 4 hours. (as described for the Shay rat). These fistula rats were then re-fed and used again 7 days later to establish gastric secretory rates for a second time.

The same general format for this research as for the Shay rat was used, namely, the following four groups: (1) Vehicle, (2) Indomethacin, (3) Vehicle plus BDL, and (4) Indomethacin plus BDL. However, there were 3 exceptions from the methods used in the Shay rat. In the chronic gastric fistula rat, (a) pylorus ligation was not performed; (b) at the termination of the 4-hour collection period, the cannulas were replugged and the animals were put back in their original feeding cages; and (c) these rats were killed 3 days later and examined for the presence of duodenal ulcers.

Duodenal Ulcer Studies

Bile Duct Ligation in Intact Rats

Indomethacin was given orally immediately after they regained consciousness from ether anesthesia after bile duct ligation. The rats were
re-fed ad libitum and were killed 3 days later. At autopsy, the stomach
and the duodenum were dissected out as one unit and examined under 2 X
magnification for ulcers. The ulcer index for each experimental group
was determined by adding the severity (on a scale from 0 - 3+), the inci-
dence, and the mean number of ulcers per stomach.

Fasting studies were also performed. Intact rats had their bile
ducts ligated after which they were either fasted (only water ad lib) or
fed for 48 hours post-BDL and indomethacin administration. These BDL
rats were then killed two days after the time of surgery and examined
for ulcers.

In order to find the optimal time period for formation of duodenal
ulcers between indomethacin administration and bile duct ligation, BDL
was performed at 0 hr, 3 hr, 8 hr, 12 hr, 24 hr, 36 hr after the rats
had been given indomethacin (15 mg/kg). All these rats were killed 3
days after indomethacin administration and examined for ulcers.

**Bile Duct Ligation in Chronic Gastric Fistula Rats**

In the chronic gastric fistula rat, the majority of the studies on
production of duodenal ulcers followed the same general format: (1)
Vehicle, (2) Indomethacin, (3) Vehicle plus BDL, and (4) Indomethacin
plus BDL. The animals were killed 3 days from the time of BDL surgery
and examined for ulcers.

Contact of gastric juice with the gastroduodenal mucosa is believed
to be necessary in order for ulcers to form. To find the interval of
time necessary for this contact to be ulcerogenic following indomethacin
administration (15 mg/kg intraduodenally) plus BDL, 60 rats were implanted
with chronic gastric fistulas. (There was a 30-minute period following
surgery plus indomethacin administration before gastric juice collection.
This was because if the cannula had been unplugged immediately after
surgery, indomethacin, given orally, would have been lost through the
gastric fistula$. The collection times of gastric juice were varied:
(1) no gastric juice collection, (2) 30 minute collection, (3) 1 hr,
(4) 2 hr, (5) 3 hr, and (6) 4 hr collection periods.

Statistical Tests

The results are expressed as means ± standard error of the mean
($\pm$ SEM) for all gastric juice values. The two-tailed Dunnett T-test
was used; significance was expressed as $p < 0.05$ and $p < 0.01$. 
RESULTS

Gastric Secretion Studies

The Pylorus Ligated Rat

Preliminary experiments were performed on rats in order to establish the best time interval between indomethacin administration and pylorus ligation. In reviewing all secretory data, it seems that most of the statistically significant results in terms of volume and acid content were obtained when indomethacin (15 mg/kg) was administered two hours before pylorus ligation and/or bile duct ligation and when gastric juice was collected for four hours post-operatively. Therefore, the format from that point forward consisted of drug dosage at -2 hr, surgery at 0 hr, and autopsy at +4 hrs.

Bile duct ligation (BDL) significantly (p < 0.01) reduced the volume of gastric juice by -68%, acid concentration by -53%, acid output by -77%, and pepsin output by -59% over the control (Vehicle-treated) group in the pylorus ligated rats. (Figures 1A, 2A, 3A, and 5A)

Indomethacin plus BDL significantly (p < 0.01) increased the volume (+30%), acid concentration (+23%) and acid output (+84%) when compared with BDL animals receiving vehicle only. (Figures 1A, 2A, and 3A)

Indomethacin without BDL did not change the volume, acid concentration or acid output of gastric juice from the control rats (Vehicle-treated). (Figures 1A, 2A, and 3A)
The Chronic Gastric Fistula Rat

The chronic gastric fistula rat as compared to the pylorus ligated rat showed an overall decrease in all components of gastric secretion. (Figures 1-5)

Bile duct ligation (BDL) significantly ($p<0.01$) reduced the volume (-57%), acid concentration (-35%), and acid output (-72%) from the sham-operated control (vehicle) group. (Figures 1B, 2B, 3B) These were similar results to those obtained in the Shay rat (except for acid concentration in the fistula rat, where there was no significant reduction). In addition, the chronic fistula rat showed no significant decrease in pepsin output from the control group as did the BDL Shay rat. (Figures 5A & 5B)

Indomethacin plus BDL significantly ($p<0.05$) increased the volume by +52%, acid output by +76% and pepsin output by +33% when compared with vehicle plus BDL treatment. (Figures 1B, 3B, and 5B)

The pepsin output was the only component of gastric secretion in the indomethacin-treated group to show a significant change (+43%) from the control (Vehicle) group. (Figure 5B)

In the basal rate studies involving over 200 chronic gastric fistula rats, the hourly secretions were as follows: 1.0 ml/1 hr, 2.4 ml/2 hrs, 3.4 ml/3 hrs, and 4.5 ml/4 hrs. The greatest hourly change - 131% - occurred between the first and second hour of gastric juice collection. (Figure 6)
Ulcer Studies

The Intact Rat and the Pylorus Ligated Rat

Duodenal Ulcers. Indomethacin plus BDL resulted in formation of acute duodenal ulcers, often perforated. The ileum and jejunum remained clear from ulcers after this treatment. Jaundice, characterized by yellow-colored skin, intensely yellow-colored urine, and yellow internal organs was always present in BDL rats.

In the fasting/feeding studies performed on intact rats with BDL plus indomethacin, fasting did not influence duodenal ulcers as compared to the fed rats, but did decrease perforations by 33%. (Table 1) Contrary to the findings of Robert, et.al. (1975) and Brodie, et.al. (1970) fasting did not reduce the incidence or severity of intestinal lesions produced by indomethacin in the intact rat. (Table 1) This reduction had been thought to be due to a decrease in bile flow during fasting.

The interval between BDL and indomethacin administration for optimal production of duodenal ulcers was investigated. Indomethacin was given to all rats at 0 time. Intact rats had their bile ducts ligated under ether anesthesia at the following time intervals following indomethacin: 0 hr, 1 hr, 3 hr, 8 hr, 12 hr, 24 hr, and 36 hrs; in one group the bile duct was not ligated. Indomethacin alone produced 100% intestinal lesions and 0% duodenal ulcers. When BDL was performed 2 hours after indomethacin, this combination (Indomethacin plus BDL) was 100% effective in producing duodenal ulcers. When BDL was performed 12 hours after giving indomethacin, the incidence of duodenal ulcers was 71%. No duodenal ulcers formed when indomethacin was administered 24 hours or longer prior to
BDL. There seemed to be an inverse correlation of duodenal ulcers to intestinal lesions. (Figure 7) There was a 40% incidence of intestinal lesions only 3 hours after indomethacin administration. It can be inferred from the data that any period greater than 12 hours between indomethacin and BDL will drastically reduce the duodeno-ulcerogenicity of the combination—BDL plus indomethacin.

Gastric Ulcers. The stomachs of the pylorus ligated rats receiving indomethacin alone showed 100% incidence of ulcers. These hemorrhagic lesions appeared in the corpus and are similar to aspirin-induced gastric lesions reported by Brodie and Chase (1967). The severity (on a scale from 0-3+) was rated at 1.4. The mean was 9 ulcers per stomach. The ulcer index of the rats receiving indomethacin alone was 20.4. Vehicle itself had no ulcerogenic effect on the stomach, neither did vehicle plus BDL. However, the stomach of the rats given indomethacin plus BDL showed 50% incidence of ulcers; 0.45 severity and 4.7 ulcers per stomach—an ulcer index of 10.2. This represents a 50% decrease from the ulcer index of the rats given indomethacin but without a BDL (20.4). Hemmati, et.al. (1974) showed that indomethacin-induced gastric mucosal ulcerations could be prevented by BDL.

Intestinal Lesions. Indomethacin alone (15 mg/kg) resulted in severe jejunal and ileal lesions within 3 days in the intact rat. These NOSAC-induced intestinal lesions were described by Kent, et.al. (1964) and Brodie, et.al. (1970). They consisted of white palpable nodules, multiple ulcers (often perforated), and adhesions to adjacent intestinal loops. Histologically, these ulcers were accompanied with inflammation, edema, and polymorpho-nuclear infiltration.
The Chronic Gastric Fistula Rat

**Duodenal Ulcers.** Interestingly, indomethacin plus BDL did not produce duodenal ulcers in the chronic gastric fistula rats, as compared to the intact rat which showed severe duodenal ulcers, although the same dosage time (-2 hours before surgery) and collection time (+4 hours after surgery) were the same. No intestinal lesions were produced in the chronic fistula rats given the combination of indomethacin plus BDL. However, the ulcer index of the stomach for this group was 4.3.

To further investigate the absence of duodenal ulcers after indomethacin plus BDL and gastric juice collection, a new population of 60 gastric fistula rats were prepared. Ten days later, indomethacin (15 mg/kg) was administered intraduodenally (ID) at the time of BDL. Gastric juice collection began 30 minutes post-operatively (because of a possible reflux of indomethacin from the duodenum to the stomach) and the collection was terminated at the following time intervals (with 10 fistula rats per each time interval): 0 min., 30 min., 1 hr, 2 hr, 3 hr, and 4 hr. Three days later, these fistula rats were killed and autopsied. Results were as follows: 100% incidence of duodenal ulcers in rats that had no gastric juice collected following BDL plus indomethacin; 80% incidence after 30 minute collection; 50% incidence after 1 hour collection; 30% after 2 hours; 37% after 3 hours; and 10% incidence of duodenal ulcers after 4 hours of collection. (Figure 8)

**Intestinal Lesions.** Indomethacin alone produced severe intestinal lesions in the chronic gastric fistula rat as in the intact rat as long as the cannula was kept closed. There was a 100% incidence of nodules, adhesions and ulcers with 75% of this group having peritoneal exudas.
Vehicle itself or in combination with BDL had no ulcerogenic effect on the stomach, duodenum, jejunum or ileum.
Volumetric Studies of Gastric Juice After 4-Hour Collection For the Pylorus Ligated Rat (A) and for the Chronic Gastric Fistula Rat (B). Standard deviation from the mean for each group is indicated by vertical bars. Significance using the Dunnett Two-Tailed T-Test is illustrated by using asterisks: * = p < 0.05 and ** = p < 0.01. The asterisks above each column indicate a significant comparison between that group and the control group vehicle alone. Asterisks located within column 2 represent a significant comparison between groups 2 and 4 - indomethacin and indomethacin plus BDL. Asterisks within column 4 represent a significant comparison between groups 3 and 4 - vehicle plus BDL and indomethacin plus BDL. This statistical format is followed in the entire result section.
FIGURE 2

Acid Concentration of Gastric Juice After 4-Hour Collection for the Pylorus Ligated Rat (A) and for the Chronic Gastric Fistula Rat (B).

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FIGURE 3

Acid Output in Gastric Juice After a 4-Hour Collection Period for the Pylorus Ligated Rat (A) and for the Chronic Gastric Fistula Rat (B).

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FIGURE 4

Pepsin Concentration in Gastric Juice After a 4-Hour Collection Period for the Pylorus Ligated Rat (A) and for the Chronic Gastric Fistula Rat (B).
FIGURE 5

Pepsin Output in Gastric Juice After 4-Hour Collection Period for the Pylorus Ligated Rat (A) and for the Chronic Gastric Fistula Rat (B).

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FIGURE 6
Hourly Basal Rate Cumulative Volume (ml) of Gastric Juice in Fistula Rats. These values represent data from 50 rats with gastric fistula implant. The greatest hourly increase occurred between the first and second hour of collection in which there was a 131% change and a 41% increase in gastric juice volume.
FIGURE 7. Time Study Investigating the Effects of Intermittently Staggered Bile Duct Ligation (BDL) Following Oral Administration of Indomethacin (15mg/kg) in Intact Rats. Results are expressed in percent incidence of duodenal ulcers and intestinal lesions.
**NOSAC**
Indomethacin

**DOSE**
15 mg/kg

**ROUTE**
Intraduodenally

**TREATMENT**
Once

**DURATION**
3 Days

---

**FIGURE 8.** Time Study Investigating the Effects of Gastric Juice Collection for Varying Time Intervals Following Indomethacin Administration Plus Bile Duct Ligation in the Chronic Fistula Rats. Cannulas were re-plugged following collection times and the rats were put in feeding cages and autopsied 3 days later.
TABLE 1. Effect of Fasting on Duodenal Ulcers, Intestinal Lesions, and Stomach ulcers

<table>
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<tr>
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<td>Administration: oral</td>
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DISCUSSION

Duodenal Ulcers

Indomethacin plus BDL in rats resulted in formation of acute duodenal ulcers which were often perforated. The pathogenesis of these duodenal ulcers was speculative. BDL by itself caused a highly significant \(p < 0.01\) reduction in gastric volume, acid concentration and output. (Figures 1-3) However, indomethacin plus BDL increased all components of gastric secretion over the control group with BDL only in both the Shay rat and the chronic gastric fistula rat. (Figures 1-5) Although indomethacin did not increase gastric acid secretion in the chronic fistula rat, the combination of indomethacin plus BDL did cause significant hypersecretion. This increase of gastric acid and pepsin plus the absence of neutralization of duodenal contents by bile may help to explain the formation of these duodenal ulcers. Pylorus ligated rats had higher values for volume and, acid and pepsin content of gastric juice than the chronic fistula rats. This supports the findings of Segal, et.al (1960) and Brodie, et.al. (1962) who suggested that pylorus ligation itself causes the rat to secrete gastric juice at maximal levels.

Formation of duodenal ulcers in BDL rats receiving indomethacin requires the following: (1) the interval between BDL and indomethacin administration must be less than 12 hours. There was a decrease in incidence of duodenal ulcers with an accompanying increase in intestinal lesions when the time between BDL and indomethacin dosage was prolonged (Figure 7); (2) Indomethacin must be at an appropriate dose. Robert,
et al. (1975) found that increasing the dose of indomethacin (doses ranging from 4 mg/kg to 15 mg/kg) in BDL rats caused progressive increases in incidence, severity, and number of duodenal ulcers; (3) Gastric juice must flow over the duodenal mucosa for a certain time period in order for ulcers to form following indomethacin plus BDL. Experiments presented by us were performed on gastric fistula rats in which gastric juice was allowed contact with the mucosa for various time intervals. The result was a decrease in incidence and severity (less perforations) of duodenal ulcers when the gastric juice collection time increased. The longer gastric juice was prevented from flowing over the duodenum, the lower the incidence of duodenal ulcers. (Figure 8)

Fasting had no ulcerogenic effect on the duodenum, jejunum or ileum. This is contrary to the findings of Brodie, et al. (1970) and Robert, et al. (1975). However, fasting increased the gastric ulcer index (13.9 vs. 9.0) when compared to fed rats. This is supportive of Dragsteit's work (1964) in which he states that food is the chief factor which protects the mucosa from its corrosive action.

From the data presented in this thesis, it seems that the pathogenesis of duodenal ulcers resulting from indomethacin plus BDL in rats is a hypersecretion of acid and pepsin combined with a decreased alkalization due to lack of bile; this differs from the pathogenesis of intestinal lesions caused by indomethacin alone.

Therefore, our experiments support the concept of the "critical" and "strategic" role of both acid and pepsin in formation of duodenal ulcers which are further aggravated by the lack of alkalinity from the bile after surgical ligation of the bile duct.
Gastric Ulcers

Our results showed that indomethacin given only produced gastric ulcers within four hours. Others have reported a similar finding. These hemorrhagic lesions produced in the corpus may be attributed to the inhibition of gastric prostaglandin synthesis, and thus, a reduction in cytoprotection of gastric mucosa. Main and Whittle (1975) found that indomethacin in ulcerogenic doses decreases the rate of mucosal blood flow per unit acid secretion, resulting in possible mucosal ischemia. They also hypothesized that production of erosions may be attributed to an increased sensitivity of the parietal cells to secretory blood flow. Main and Whittle (1975) stated that pre-treatment with indomethacin potentiated the secretory response to dibutyryl cyclic adenosine monophosphate. Chaudhury (1976) suggested that indomethacin acts on the active transport mechanism of the gastric mucosa by inhibiting the gastric mucosal sodium pump. The ulcer index of the rats given indomethacin alone was 100% higher than the indomethacin plus BDL-treated animals (20.4 vs. 10.2, respectively). This is, to a degree, supportive of the work done by Hemmatti, et.al. (1975) who found that BDL prevents indomethacin-induced gastric ulceration. Indomethacin-treated gastric ulcers may also be due to a reflex of bile acids into the stomach, a common occurrence in gastric ulcer patients (Brodie, 1974) and also in rats (Forough, et.al. 1975); these bile acids could then break the mucosal barrier. Studies by Rhodes, et.al. (1972) indicated that bile acids could impair the normal barrier to back diffusion of acid.

However, BDL rats given indomethacin also developed gastric ulcers although to a lesser extent than the animals given indomethacin alone.
Indomethacin was shown to significantly increase pepsin output in both groups — indomethacin alone and indomethacin plus BDL — over the control. (Figure 5)

**Intestinal Lesions**

Indomethacin, like other non-steroidal anti-inflammatory compounds, produced severe jejunal and ileal lesions within 2 to 3 days when given at high doses. These lesions are believed to be due to inhibition of prostaglandin synthetase activity and subsequently, a deficiency in prostaglandins (Kent, et al., 1969; Vane, 1971; Flores and Sharp, 1972; Karppanen and Puurunen, 1974; Main and Whittle, 1975; Robert, et al., 1975; and Robert, et al., 1976). It has been shown that prostaglandins afford cytoprotection against these indomethacin-induced lesions (Robert, et al., 1975). In addition, a NOSAC may lead to increased susceptibility of the small intestine to noxious agents present in the intestinal contents (Robert, et al., 1975). Kent, et al. (1969) suggested that the bacterial flora plays an important role in the development of intestinal ulcers, since antibiotics reduce such lesions.

Indomethacin-induced intestinal lesions were not caused by acid secretion, since there was no gastric juice in the jejunum and ileum. This was supported by the fact that antacids, i.e., Malcogel® and anticholinergics, such as, methscopolamine bromide, did not inhibit indomethacin-induced intestinal lesions.

Bile plays a role in the formation of NOSAC-induced intestinal lesions. Hucker, et al. (1970) found that indomethacin is metabolized in the rat via \( N \)-debenzylation and O-demethylation resulting in extensive biliary excretion of indomethacin metabolites. An enterohepatic cycle develops where the drug is excreted in the bile and reabsorbed by the gut.
Brodie, et al. (1969) have shown that indomethacin or a metabolite of indomethacin in bile had to be present in order for perforations to occur. The reduction of bile flow was shown to be directly related to a reduction of intestinal perforations following indomethacin administration. BDL inhibited formation of the indomethacin-induced intestinal lesions. This result may partially be explained in that after the bile duct is ligated, no more bile carrying indomethacin flows into the intestine so that lesions do not form (Brodie, et al., 1970).
CONCLUSIONS

1. Indomethacin (15 mg/kg) given orally 2 hours before BDL produced duodenal ulcers in the rat within 3 days, and no intestinal lesions occurred as they did with indomethacin alone. This may be due to an absence of bile carrying the indomethacin into the intestine, so intestinal lesions do not form. (Figure 7)

2. Oral administration of indomethacin (15 mg/kg), a non-steroidal anti-inflammatory compound (NOSAC) produced severe jejunal and ileal lesions within 3 days, as shown by others. (Table 1)

3. The pathogenesis of indomethacin-induced intestinal lesions was different from that of duodenal ulcers caused by indomethacin plus BDL. From these experiments it was shown that indomethacin plus BDL result in significant increases of gastric volume, acid and pepsin content as compared to the controls of BDL plus vehicle in the Shay rat and to a lesser degree in the chronic gastric fistula rat. (Figures 1-5)

4. Bile duct ligation alone significantly reduced the volume, acid concentration and acid output of gastric juice in both the pylorus ligated rat and the chronic gastric fistula rat (except for acid concentration in the fistula rat where there was no significant reduction).

5. Indomethacin plus BDL appeared to produce duodenal ulcers in rats because of hypersecretion of acid and pepsin. In addition, with the bile duct ligated in these rats, there was an accompanying absence of neutralization of duodenal contents by bile.
6. The proposed mechanism(s) of action of the ulcerogenic effect of indomethacin on the intestine is believed to be by the following:
(a) inhibition of prostaglandin synthetase; and, (b) extensive biliary excretion of indomethacin.
REFERENCES


