Lack of Cytoprotection by Acetaminophen against Ethanol-,
HCl-Ethanol- and HCl•Aspirin-Induced Gastric Mucosal
Lesions in Rats

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Abstract—Effects of acetaminophen against gastric mucosal lesions induced by
three different necrotizing agents were studied. Acetaminophen (30, 100 mg/kg),
given p.o. 0.5 hr before absolute ethanol, HCl-ethanol, or HCl-aspirin adminis-
tration, afforded no cytoprotection against gastric mucosal lesions induced by the
above agents in 24 hr fasted rats. However, 16,16-dimethyl prostaglandin E₂
(3 μg/kg), given p.o. 0.5 hr before these necrotizing agents, completely prevented
development of these lesions.

There are various agents, including prostaglandin analogs, which protect the gastric
mucosa against damage induced by necrotizing agents such as absolute ethanol, a
strong acid or alkali (1, 2). Several groups (3–5) reported that acetaminophen, an analgesic
drug, is also a cytoprotective agent because it prevented the development of gastric mucosal lesions induced by 20% or absolute ethanol or acidified aspirin in animals and man. However, other groups (6, 7) have
recently failed to obtain evidence that acetaminophen has a cytoprotective activity
against aspirin and ibuprophen-induced gastric mucosal lesions in man. Therefore, we
re-examined in rats the effect of acetaminophen on gastric lesion models induced by
absolute ethanol, HCl-ethanol, and HCl-aspirin. 16,16-Dimethyl prostaglandin E₂
(dmPGE₂), an agent of proven efficacy against these lesions, was used as a positive
control.

Male Sprague-Dawley rats (220–250 g) were deprived of food for 24 hr before the
experiments. Water was given freely for the initial 22 hr, but was withheld for 2 hr before the start of the experiments. These rats were kept in raised mesh-bottomed cages to prevent coprophagy. Eight rats were used for each study. Gastric mucosal lesions were produced by giving p.o. 1 ml/200 g body wt. of absolute ethanol (v/v) (1), 60% ethanol (v/v) in 150 mM (HCl-ethanol) (8, 9), or aspirin (150 mg/kg, Nakarai) in 150 mM HCl (HCl-aspirin) (10). The rats were killed 1 hr later, the stomachs were removed, inflated by injecting 8 ml of 2% formalin, and im-
mersed for 10 min in 2% formalin to fix the gastric wall. The stomachs were then incised
along the greater curvature and macro-
scopically examined for lesions. The length (mm) of each lesion was measured under a
dissecting microscope (x10) with a square
grid, and the total length per stomach was calculated. The person (S. O.) measuring
the lesions did not know the treatment given
to the animals. Acetaminophen (Sigma) was
suspended in saline with a trace of Tween
80. dmPGE₂ (Ono) was first dissolved in
absolute ethanol (1 mg/ml) and then diluted
in saline before use. Acetaminophen (30 or
100 mg/kg) or dmPGE₂ (3 μg/kg) was
given p.o. in a volume of 1 ml/200 g body wt.
0.5 hr before absolute ethanol, HCl-ethanol,
or HCl-aspirin administration. The vehicle
alone was given to the control animals.
Student's t-test was used to determine the
statistical significance of the data, and a
P<0.05 value was regarded as significant. All
data represent the mean±one S.E.M.

In all control animals given absolute ethanol, HCl-ethanol, or HCl-aspirin, multiple,
elongated bands of lesions in the glandular stomach appeared 1 hr later. The degree of lesion formation differed with the necrotizing agent used. The mean lesion length was 61.6±16.3 mm (absolute ethanol), 84.8±9.3 mm (HCl·ethanol), and 26.4±6.3 mm (HCl·aspirin). Pretreatment with acetaminophen (30 and 100 mg/kg) did not protect the gastric mucosa against the damaging effects of the above three necrotizing agents (Figs. 1 and 2). In contrast, dmPGE2 (3 μg/kg) completely protected

![Figure 1](image1.png)

**Fig. 1.** Effects of acetaminophen (AC) and 16,16-dimethyl prostaglandin E2 (dmPGE2) on absolute ethanol-, HCl·ethanol- and HCl·aspirin-induced gastric lesions in rats. AC and dmPGE2 were given p.o. 0.5 hr before administration of the above necrotizing agents. Animals were killed 1 hr after administration of necrotizing agents. AC, in contrast to dmPGE2, had no protective effect on the development of three types of lesion models. Data represent the mean±one S.E.M.

![Figure 2](image2.png)

**Fig. 2.** Gross appearances of the stomachs of rats treated with the vehicle plus absolute ethanol (left) and acetaminophen (AC, 100 mg/kg, p.o.) plus absolute ethanol (right). Note that there was no macroscopic difference between the control and AC treated stomachs.
the gastric mucosa against these so-induced lesions, regardless of the necrotizing agents. This study showed that in contrast to the earlier studies (3-5), acetaminophen had no cytoprotective effect on three different lesion models in rats. It is hard to explain this apparent discrepancy between our data and those of others. Seegers et al. (3) demonstrated that acetaminophen at 60 and 125 mg/kg given together with aspirin at 60 and 125 mg/kg clearly protected the gastric mucosa against aspirin-induced lesions by 61.7% and 88.5%, respectively. They observed the gastric mucosa 17 hr after p.o. administration of aspirin or aspirin plus acetaminophen. Recently, it was found that gastric mucosal lesions acutely induced by ethanol rapidly recover (within 2 hr) and that dmPGE2 enhances the recovery process (11-13). Therefore, it is possible that although they used aspirin to damage the gastric mucosa, the protection observed by Seegers et al. (3) is not due to prevention of lesion formation, but is rather due to enhancement of the once damaged mucosa. The same may apply to the results of Konturek et al. (4) who determined the protective effect of acetaminophen against aspirin-induced lesions 3 hr later. However, they showed in the same report that pretreatment with acetaminophen (80 mg/kg, p.o.) almost completely protected the gastric mucosa against the damaging effect of ethanol 1 hr after its administration. These results would suggest that acetaminophen protection observed by these investigators, at least with regard to the ethanol-induced lesions, is not due to an enhancement in the recovery of the damaged mucosa.

Konturek et al. (4) and Stern et al. (5) reported that the mechanism responsible for acetaminophen cytoprotection may be mediated by an increased endogenous prostaglandin synthesis, because indomethacin abolished the effects. One possible explanation is that the rats they used (Wistar, female or both sexes) may have a high susceptibility to acetaminophen and hence an increase in endogenous prostaglandin levels compared to our rats. It has been repeatedly confirmed that dmPGE2 protects the gastric mucosa against mucosal lesions induced by various necrotizing agents (1, 14). We also confirmed that dmPGE2 exerted protective effects on these lesion models under the conditions of our present study. Our data are consistent with those of Graham and Smith (6) and Lanza et al. (7) who found no clinical cytoprotective effects of acetaminophen.

We conclude that in rats acetaminophen has no cytoprotective effect against gastric mucosal lesions induced by necrotizing agents.

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