Early Gastric Vascular Damage caused by different Noxious Agents in Rats

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Abstract
Leakage of intravenously administered Evans blue dye into glandular stomach and gastric contents of rats was measured spectrophotometrically in order to quantify early vascular damage induced by various noxious agents and stress. As compared to control rats, significantly higher quantities of Evans blue were found to leak into the stomach and contents following 10 min exposure to 100 mg/kg acetyl salicylic acid (ASA). 100 mg/kg soluble ASA and 1 ml of 100% ethanol as well as 1 hour exposure to cold immobilization stress. A dose response curve was constructed for ASA induced damage. Pretreatment with sucralose significantly reduced ASA induced damage. Thus, an increased vascular permeability seems to be a common early feature in the pathogenesis of gastric mucosal damage produced by different noxious agents.

Key Words: Acetyl salicylic acid, ethanol, gastric vascular damage, stress.

Introduction
Increased gastric vascular permeability has been shown in rats to precede gross mucosal erosions after exposure to ethanol.1 It has also been established that gastric mucosal ischaemia plays an important role in drug2 as well as hypothermic3 and hypovolemic4 stress induced mucosal damage. Hypothermia has been further shown to lead to increased capillary permeability as measured by the lymph to plasma protein concentration ratio and lymph fluid.6 In the present study we wanted to find out whether a short exposure to various noxious agents like acetyl salicylic acid (ASA), soluble ASA (Disprin), ethanol and exposure to cold immobilization stress produced increased capillary permeability indicating early gastric vascular damage. We also investigated whether sucralose, a known cytoprotective drug,7 prevented ASA induced early vascular damage.

Material and Methods
The study was performed in 3 parts:
1. Ethanol and salicylates model: Adult rats of either sex weighing from 150-200 g were used for this study.

2. Cold immobilization stress model: Another group of 6 animals was studied for the effects of cold immobilization stress. These animals were restrained on an inclined plane at an angle of 45°, head low, at a temperature of 4° C for a period of 1 hour. The stress period of 1 hour was selected in preference to 2 hours in order to achieve early gastric mucosal damage, since stress of 2 hours is known to lead to gross mucosal lesions.8 The rats were then removed to room temperature and anaesthetized. Evans blue was injected in the femoral vein and the procedure described earlier was followed.

3. Cytoprotection with sucralose: In the animals studied for the cytoprotective effect of sucralose, a fresh suspension of sucralose was administered in a dose of 100 mg/kg intragastrically 15 min before the injection of Evans blue and the animals were killed 10 min later. The stomachs and contents were processed as before.
Results
The mean ± SE Evan’s blue level in the glandular stomach of control animals given 1 ml distilled water intragastrically was 4.49 ± 1.39 μg/g. The level in the gastric contents was 0.586 ± 0.208 μg/g in these animals.

As compared to these animals the Evan’s blue in the glandular stomach (13.86 ± 2.48; p < 0.001) and gastric contents (2.951 ± 0.212; p < 0.001) were significantly higher in the ASA (100 mg/kg) treated group. Similarly, when the animals received 1 ml of 100% ethanol, the glandular stomach had 4.8 ± 1.42 (p < 0.001) and gastric contents 6.26 ± 1.55 μg/g (p < 0.001) Evan’s blue. A significantly increased quantity of Evan’s blue was found in the glandular stomach and contents of animals given 100 mg/kg Disporin and cold immobilization stress. There was a linear correlation (r = 0.9977) between the logarithm of the dose of ASA and the quantity of Evan’s blue in the glandular stomach.

When the animals were treated with sucralfate prior to exposure to ASA (100 mg/kg), Evan’s blue content in the glandular stomach (1.822 ± 0.944; p < 0.001) and gastric contents (0.67 ± 0.102; p < 0.001) was significantly lower than in animals given ASA alone.

Discussion
We have demonstrated that acetylsalicylic acid (ASA), its soluble form Disporin (100 mg/kg), 1 h cold immobilization stress and ethanol (1 ml of 100%), all produce comparable early gastric vascular damage as shown by increased leakage of Evan’s blue dye into the glandular stomach and gastric contents. A dose response relationship has also been demonstrated with ASA. Our results therefore support and extend the observation of Szabo et al on this model. Sucralfate pre-treatment caused a significant reduction in the Evan’s blue levels in the glandular stomach and gastric contents indicating protection against ASA induced mucosal damage. The levels of Evan’s blue were even lower than the values obtained in control animals.

Other cytoprotective drugs like prostaglandins have previously been shown to protect against ethanol induced gastric mucosal barrier damage in this model.

Thus, our results indicate that early vascular injury leading to increased capillary permeability plays a role in the pathogenesis of mucosal damage with various noxious agents like acetyl salicylic acid, ethanol and cold immobilization stress.

References