Introduction

It is well known that various nutritional supplements, particularly hyperosmolar glucose, prevent development of stress-induced ulcers in rats and that glucose treatment has been found to be more effective than antacids, H₂ receptor blockers and other medicines (1-4). There is clear evidence that stress ulcers formation (and subsequent bleeding) is caused by excessive gastric acid secretion (5), mucosal ischemia (6), mucosal metabolic energy deficit due to lack of nutrients (7), and possibly an increased permeability to hydrogen ions (8). Various explanations about the protective effect of hyperosmolar solutions exist. Some authors argue that these solutions prevent stress ulcers in rats due to increased endogenous prostaglandins in their gastric mucosa (9). Others propose that hyperosmolar glucose supports energy metabolism by direct absorption from the gastric cell but this mechanism has not been proven yet (9,10), while still other authors suggest that glucose is not absorbed from the gastric mucosa (11, 12). We observed in our previous study that intragastric administration of 30% glucose and fructose solutions was absorbed and had a protective effect on stress ulcers as determined by macroscopic evaluations (13, 14). But it was not clear if this absorption originated from gastric absorption of glucose or dilution of glucose in the gastric lumen. To overcome the dilutional factor of the glucose within the stomach, we planned this experimental study to accurately estimate the C14 glucose absorption rate from the gastric lumen directly.

Material and Methods

The experiment was performed on 22 Swiss-Albino type rats of 160-190 gr. All rats were conditioned for two months on standard rat chow and water. The rats were not given any food, only water, during the last 24 hours before the experiment. Their abdomens were opened by an upper median incision, under ether anaesthesia. Cardia and pylorus were ligated using silk sutures. The stomach was then washed with physiological serum and the contents were aspirated. The rats were divided into 3 groups:

A) Rats given 4 ml glucose solution of 30% + 0.6 ml C14 labelled glucose solution (n=6),
B) Rats given 4 ml glucose solution of 30% + 0.6 ml C14 labelled glucose solution + stress and exposed to cold (n=8),
C) Rats given 4 ml physiologic serum + 0.6 ml solutions were absorbed and had a protective effect on stress ulcers as determined by macroscopic evaluations (13, 14). But it
How Hyperosmolar Solutions (Glucose 30%) May Prevent Stress Induced Ulcers in Rats

The others (groups B and C) were kept under cold restrained stress for four hours. At the end of the fourth hour, the rats were sacrificed by an intracardiac injection of sodium pentobarbiturate. The contents in their stomachs were aspirated, their volumes were determined and they were put under deep freeze. The stomach of each animal was removed en bloc, opened along great curvature and spread out on blocks of paraffin. They were washed with physiologic serum, dried by air and the lesions were examined under a dissecting microscope by a pathologist unaware of the treatment groups. Lesions were graded by the Scheric method (15-16). Ulcer indexes were found by dividing length by number of lesions.

C14 labelled glucose solution + stress and exposed to cold (n=7).

After these solutions were given and irrigated to the stomach, 1ml of these solutions were aspirated for a background count of each group.

Preparation of the C14-labelled glucose solution was according to the following procedure: D glucose-UL 14C (Sigma G 4395, 6 mCi/mmol, 0.1 mCi/ml in aqueus sol.) was used for this experiment. 2 ml of D-Glucose-UL 14C were added to 18 ml physiologic serum. Then, 0.6 ml from this solution were used for each animal.

The rats in group A were placed in their cages and

Figure 1. Ulcer Indexes in the groups
* The differences between groups A and C (p<.01), B and C (P<.05) were significant, A and B (p>.05) was insignificant.

Figure 2. Net Absorption Rates of C14 Glucose in the groups
** The differences between all groups were significant (p<.01)
Results

At the end of the experiment, twenty one rats were alive. One rat died due to ether anaesthesia. Ulcer indexes were the lowest for group A (administered 30% glucose and unstressed) and the highest for group C (administered physiologic serum and stressed). The differences in ulcer indexes between groups B and C (p<.05), and A and C (p<.01) were significant. But, no significant difference was found between groups A and B (Fig. 1).

C14-labelled glucose was found to be absorbed throughout the gastric mucosa in all three groups. The absorption rates of glucose in group C were highest and lowest in group A. The differences in absorption rates between all groups were statistically significant (p<.01) (Fig. 2).
The differences in C14-labelled glucose level of gastric samples (in both nonulcerative and ulcerative areas) between groups were not statistically significant (p>0.05). So, stomach glucose levels were taken as the average levels for ulcerated and intact areas of the gastric samples. The mean distribution level of the gastric walls was significantly higher than those of other tissues; liver, ileum, spleen, and kidney (p<0.01). The mean diffusion rate of group B was significantly different than those of other groups (p<0.05). In addition, Figure 3 shows distribution level of C14 labelled glucose for ileum, liver, spleen and kidney. The distribution levels of glucose in the various other tissues were not significantly different from each other, and they are negligible.

**Discussion**

Tube feeding diminishes the incidence of stress bleeding in several types of critically ill patients (17). The physiopathology of stress ulceration is complex and multifactorial. The factors such as secretion of gastric acid (5), mucosal ischemia (6), deficiency of metabolic energy (7) and vasoactive substances as histamin and serotonin due to increasing of H+ permeability (8) are the possible causes of the ulcers. So, the prophylaxis and treatment of stress ulcers are still not clear yet.

In the present experimental study, 30 percent glucose showed a protective effect from stress-induced ulcers in rats (Fig 1). But the effect of 30% glucose is by a mechanism other than neutralizing ions, since the acid buffering capacity of 30% glucose is equivalent to normal saline solution, a solution with no prophylactic effect in the rat restraint model (11). Intragastric administration of 30 percent glucose may have several physiologic effects relevant to its prophylaxis of stress ulceration: systemic absorption and utilization of glucose, elevation of endogen prostaglandins, administration of volume, direct supply of the glucose solution to the gastric mucosa (12).

It is important note that systemic absorption and utilization of glucose was impossible in our experiment because the pylorus and cardias of the rats were ligated.

Elevation of endogen prostaglandins in the gastric wall may have an effect on the prevention of stress ulcers. Since many prostaglandins possess potent vasoactive properties, enhancement of gastric mucosal blood flow by these agents may play an important role in mediating cytoprotection. A number of prostaglandins are known to exhibit potent vasodilatory actions and affect various vascular beds throughout the body, including those of the gastrointestinal tract. These vasoactive effects are especially evident during parenteral administration and often occur quickly after injection (9). Ephgrave et al. (10) concluded that endogen prostaglandins were useful in gastric mucosal defense but were not necessary for the protection afforded by 30% glucose. They also suggested that 30% glucose was absorbed directly through the gastric mucosa. But the same authors in another experimental study (12) argued that hyperosmolar glucose increased intragastric volume and intraluminal pH. They postulated that these factors may contribute to the protection of gastric mucosa from stress ulceration.

From an experimental study like ours, Mullane J.F. et al concluded that no substantial transport of intraluminal glucose from the stomach occurred (11). They argued that glucose was not directly absorbed through the gastric wall. But they did not directly estimate glucose absorption rate by glycerol or radioactive glucose, they measured only intragastric concentration of glucose so they have used an empirical method.

In our previous investigation (13, 14) we did not estimate the glucose absorption rate by using glycerol or radioactive glucose. We observed that glucose was absorbed and that energy charges were elevated in the gastric mucosa. We performed this study to accurately estimate the absorption rates of glucose throughout gastric mucosa.

C14-glucose was absorbed through the gastric wall in all groups and the difference in absorption between the groups was statistically significant (p<0.05, Fig 2).

While absorption in the nonstressed group with administration of 30% glucose was 12.23±4.8 %, the application of stress increased absorption to 23.01±8.3 %, and this was related to mucosal energy deficiency and defect in the mucosal barrier. Absorption rate in the stress applied group with physiological serum, was 53.19±4.65 %. This was referred to the fact that C14-glucose concentration in this group was low as compared to the other groups, in contrast to the hunger of the gastric mucosa for energy. In addition, sodium concentration in the stress applied group with physiological serum (group C) was highest. So, sodium and glucose cotransport or symport
(Na+ dependent glucose transport, SG Cotransporter) may facilitate diffusion of the glucose molecules (19).

The difference in distribution of the C14 glucose between the stomach and other tissues was significant (p<.01, Fig. 3). The estimated the C14 radioactivity in the gastric wall was highest in group B and lowest in group C. Despite the fact that the absorption rate within the stomach was highest in group C (53.2%), level of the C14-labelled glucose in the gastric wall was the lowest in the C group (8.03 %). This can be explained by the fact that there was only C14 labelled glucose in the lumen of the stomach in this group, so we postulated that there was a greater utilization of the absorbed glucose. This hypothesis could be supported by estimation of the radioactivity in the expired air, but we did not measure it. The distribution of C14 glucose in the ileum and the other tissues were much lower and not statistically significant (Fig.3). These results show that glucose is absorbed directly through the gastric wall, but not through the ileum and distal gastrointestinal tract, and that it protected rats from stress-induced ulcers.

References