The Effect of Single Dose H2-Receptor Antagonist (Cimetidine) on Rat's Hepatic Blood Flow

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Summary: *Conflicting data exists regarding the effect of the H2-receptor blocking agent cimetidine on hepatic blood flow. The acute effects of cimetidine on hepatic blood flow were studied in fifteen (Mus. Norvegius Albinos) rats. Administration of (25mg.kg.-1) and (50mg.kg.-1) cimetidine reduced hepatic blood flow.*

Key Words: H2-receptor antagonist, cimetidine, hepatic blood flow, rat's liver, experiment.

Discovery of H2-receptor blockers by Black and colleagues, provided a more specific type of inhibitors for gastric acid secretion. (1,7,13). The use of cimetidine has been approved by The Food and Drug Administration, for the treatment of duodenal ulcers, the Zollinger-Ellison syndrome and other gastric hypersecretory states, since 1977. (3).

It was observed that by using the Indocyanine green (ICG) elimination test, cimetidine reduces the liver blood flow in human subjects. (3,.6,7,8,12). However, there is a lot of contradictory data from other investigators who also used the ICG elimination test. (1,2,4,5). For that reason, we prefered to study from a different point of view that being to examine whether cimetidine reduces the liver blood flow. For, that purpose, in our experimental study, liver tissue oxygenation was directly measured using polarographic technique.

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RESULTS DISCUSSION

As many of us know, changes of one of the tissue's blood flow cause change to oxygenation of that tissue. Therefore, invivo measurement of oxygen from a tissue may give some information about the blood flow of that tissue. In this experimental study, our aim was to evaluete hepatic blood flow by comparing liver tissue oxygen concentration. Since, the dosage (106-150 mg.kg.-1 iv) is LD50 for the rats (14), we did give a (25 mg.kg.-1) and (50mg.kg.-1) cimetidine, in our experiment.

In this experiment, using polarographic technique, it was observed that (25 mg.kg.-1) and (50 mg.kg.-1) doses of cimetidine, significantly reduced the liver oxygenation by %33 and %45 respectivelly, when compared with placebo (serum phsiologic: SP), by t-test. (Fig.1: $p<0,01$ and Fig.2:$p<0,001$).

From this data, it may be concluded that cimetidine reduces the liver blood flow. In order to decide whether the effect of cimetidine was systemic or regional, gracilis muscle oxygenation was measured as well. In that group, we observed that cimetidine also diminished the skeletal muscle oxygenation significantly (%30) when compared with placebo. (Fig.3:$p<0,001$).

After administration of cimetidine and observation of a decrease in oxygen, either in liver or skeletal muscle, we concluded it resulted from the systemic effect of cimetidine.

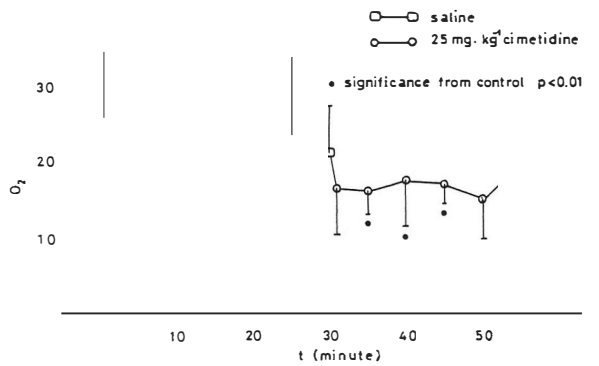

Fig.1: The effect of 25mg. kg-1 cimetidine on liver oxygenation

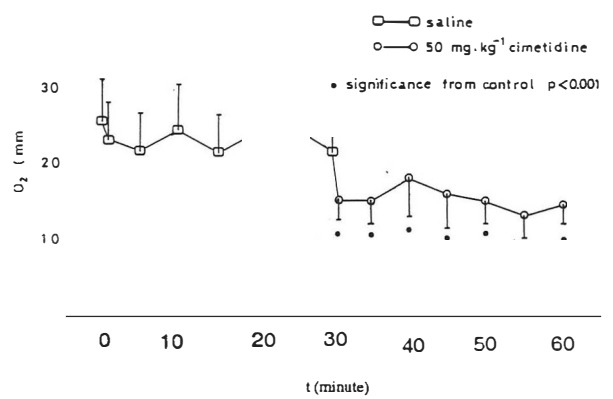

Fig. 2: The effect of 50 mg.kg-1 cimetidine on liver oxygenation

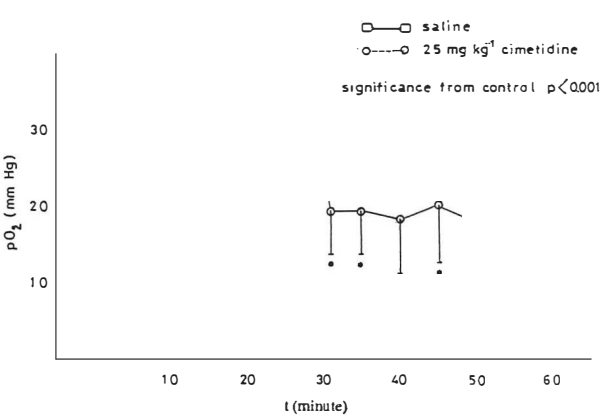

Fig.3: The effect of 25mg.kg-1 cimetidine on skletal musole mass

Despite the reducing effect of cimetidine on liver tissue oxygenation, we did not observe any histopathologic pattern of ischemia in the tissue specimens. This observation probably resulted from either single dose administration or short time exposure.

First, Feely et al. reported that cimetidine reduces liver blood flow measured by ICG clearence in normal volunteers and concluded that cimetidine caused %25 reduction in hepatic blood flow. (1). But, some authers concluded that, the fall in ICG clearence on cimetidine could have occured as a result of altered metabolism and reduced hepatic extraction and may not reflect a reduction in hepatic blood flow. (3,6,7).

In recent years, studies in the volunteers which were mostly ICG clearence dependent showed that cimetidine had not changed hepatic blood flow in healty people. (1,2,4,5). On the other hand, some studies showed that in the healty people, hepatic blood flow did not change. But, patients with chronic liver diseases exhibited some changes in hepatic blood flow. (3,11). Yet, other studies did not confirm this result. (1,4,8,10,12). One may conclude the matter remains open to discussion and there is some contradiction.

The results of our study are similiar to those of the other studies about reduction of liver blood flow by cimetidine (1,3,11), and H2-receptor blockers have a significant effect on the hepatic and peripheric blood flow. (3,6,9,11). We belived this effect is due to-most probably-blocking histamin-2 receptors, resulting in a systemic effect. For this reason, we suggest it is better not to give H2-receptor blocker drugs, to those individual who have hepatocelluler disease and are peripheric vascular insufficient.

EXPERIMENTAL

Material:
Fifteen male (Mus. Norvegius Albinos) rats with a mean age of 10 weeks and mean weight of 200 gr. (195+- 20gr) were used for three experimental groups. Each rat of the experimental groups were used as well as their own control groups. All rats had normal diet before experiment. There were three experimental groups:

1. (25 mg.kg.-1) cimetidine, iv bolus: n:5
2. (50mg.kg.-1) cimetidine, iv bolus: n:5
3. (25mg.kg.-1) cimetidine, iv bolus, tissue oxygen measured from gracilis muscle :n:5

PROCEDURE

Anaesthesia was induced and maintained with urethan (1,5 mg.kg.-1 ip.). Tracheostomy was performed in order to eliminate the probabilty of respiratory distress which may be due to secretion. One of the jugular vein was cannulated for drug administration. In our study, after 20 minutes, oxygen concentration values remained stable because of the limited observation period to 30 minutes.

Tissue oxygenation was continuously monitored, polarographically, by using collodion-coated open-type glod electrodes placed on the liver and the gracilis muscle surface (Tacussel PRG-DEL unite Amperometrique).

After preparing the liver and gracilis muscle, a gold electrode was placed on these tissues without demaging the cells and without obstructing the blood flow. At the beginning of the experiment each rat was given SP in equal volume of cimetidine. Doing this provided a self-control. After recording initial liver and muscle tissue oxygenation on equivalent volume of SP was administred through venous catheter. Than every 5 minutes were recorded tissue oxygenation values. Following this, for the first group (25mg.kg.-1) and for the second group (50 mg.kg.-1) cimetidine was administred. The same recording was applied for the cimetidine.

At the end of experiments we took samples from liver for the hystopathologic examination.

Statistical analyses were carried out by the Student's t-test and analysis of variance.

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