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EVALUTION OF CIMETIDINE AND RANITIDINE DOSES FOR POTENTIAL EFFECT ON GLUCOSE UTILIZATION IN NORMAL AND ULCERATED RATS

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ABSTRACT

The ability of the body to utilize glucose may be ascertained by measuring its glucose tolerance . The present work was devoted to study the role of different therapeutic doses of cimetidine and ranitidine on glucose utilization in normal and gastrointestinal-induced ulcer in rats . Two groups of male albino rats were used in this study , one received three oral cimetidine doses, (54 mg kg^{-1}, 108 mg kg^{-1} and 216 mg kg^{-1}, respectively). The second group was given three oral ranitidine doses(13.5 mg kg^{-1}, 27 mg kg^{-1}, 54 mg kg^{-1}, respectively) which they comparable to a half, and double daily human therapeutic doses . Rats in each group served as their own control and doses were given in three successive trials , carried out at weekly intervals , prior to oral determinations revealed that the marked increase in glucose tolerance were glucose load of 1.0 g kg^{-1} b.wt. Serial post loading parallel to the rising therapeutic doses of cimetidine and ranitidine. Induction of gastrointestinal ulcer in a group of rats subjected to treatment with oral dose of 10 mg kg^{-1} indomethacin for five successive days and then treated with both drugs for three months, revealed a common significant decrease in monthly recorded serum glucose. The magnitude of the decrease parallel to the increasing therapeutic doses of both drugs .

Finely we concluded that, careful attention should be taken before treatment with these drugs , especially for individuals with lower blood glucose level or diabetic patients suffering from gastric ulcers.

INTRODUCTION

The pathophysiology of acid- peptic disease may be thought as an imbalance between aggressive factors (acid , pepsin, *Helcobacter pylori* infection) and local mucosal defenses (secretion of bicarbonate , mucus and prostaglandins) (1).

Therapeutic strategies are aimed at balancing aggressive factors against defensive or cytoprotective factors. Drugs that reduce gastric acid secretion (H_2 histamine receptor antagonists and covalent inhibitors of H^+ , K^+ - ATPase of parietal cell) effectively promote healing. Cytoprotective agent (sucralfate , colloidal bismuth, prostaglandin agonist (misoprostol) and antacids also are effective (2).

Cimetidine and ranitidine are a histamine H_2-receptor antagonist they used in the management of various gastro - intestinal disorders such as aspiration syndromes, dyspepsia, gastro-esophageal reflex disease, peptic ulceration and Zollinger-Ellison syndrome, (3).

This investigation aimed at explaining the interference of antacid drugs with glucose utilization especially in case of gastrointestinal ulcer diseases.

EXPERIMENTAL DESIGN

Two groups of 10 adult male albino rats, weighing 180 - 200 g were used in this study. The animals in each group served as their own control, and were subjected to four successive experimental trials, carried out at weekly intervals each entailing oral glucose loading to rats in amounts of 1g kg^{-1} b.wt. administered as 10% aqueous solution. The first trial in each group provided blank control data for serum glucose determination , initially after 14 hours fasting period , and subsequently after lapse of 1, 1.5 , 2 and 4 hours following oral glucose load. In the second , third and fourth repetitive trials in each group. Cimetidine was given in single oral dose 2 hours prior to glucose loading equivalent to half (54 mg kg^{-1}), daily (108 mg kg^{-1}) and double (216 mg kg^{-1}) the human daily therapeutic dose (1200 mg) . Animals of the second group were treated similarly using ranitidine in doses equivalent to half (13.5 mg kg^{-1}), daily (27 mg kg^{-1}) and double daily (54 mg kg^{-1}), the human daily therapeutic dose (300 mg).

Venous blood samples were obtained from the retro orbital plexus of the rats , in accordance with **Schermer** (4) techniques. Serum was separated and rapidly subjected to glucose determination according to **Trinder** (5) method.

Induction of gastrointestinal ulcer :

A group of 60 adult male rats with average body weight (180 - 200 g) , were subjected to oral daily dose of 10 mg kg^{-1} indomethacin for five successive days (6). Gastrointestinal ulceration was conformed by histopathological examination of stomach section stained with haematoxylin and eosin (H & E) (7) (Figs. A & B) .

The animals were then divided into two groups. Each group was divided into three subgroups (n = 10

each) . The first three subgroups were treated with cimetidine in a doses equivalent to half , daily and double daily human therapeutic dose. The second three subgroups were treated with ranitidine in doses equivalent to half , daily and double daily human therapeutic dose. Blood samples were collected from each rat before and after induction of gastrointestinal ulcer and then at monthly intervals for three months. Serum glucose estimation were done in all blood samples as before .

Paired student's "t" test of statistical significance [8] was adapted for analysis of the results.

RESULTS

As illustrated in Fig. (1), ranitidine treatment showed marked increases in oral glucose tolerance, this increase was parallel with rise of doses as verified by lower magnitude of post loading hyperglycemia, comparable with control value, given rise to a very highly significant peak value with 2 P<0.001 amounted to 129.9 mg%, 121.26 mg% and 101.2 mg% respectively in case of half , daily and double human therapeutic daily dose (300 mg) , compared with 146.09 mg% in case of control .

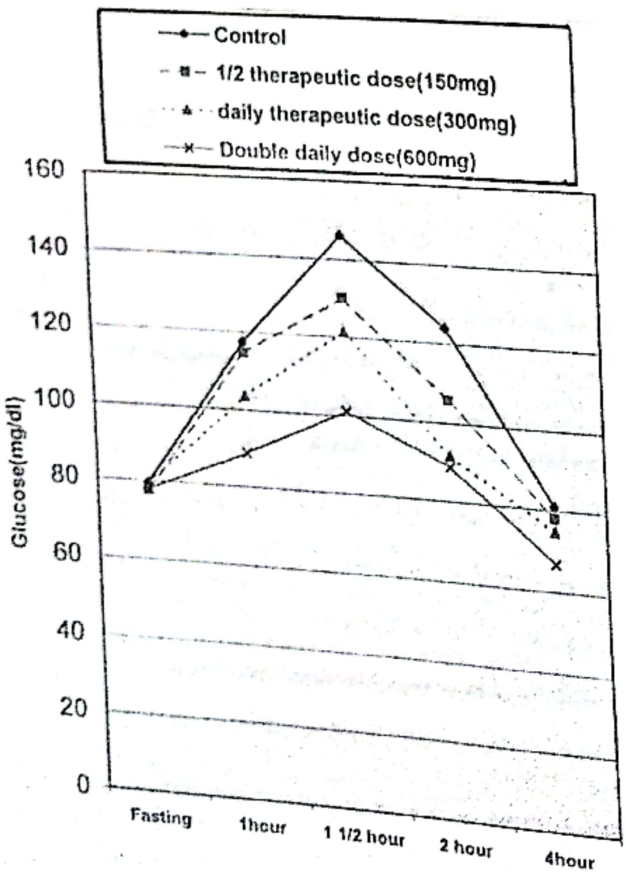

Fig.(1): Glucose tolerance curves after therapeutic doses of rantidine for adult male albino rats (n= 10 rats).

On the other hand , it is apparent from Fig. (2), that cimetidine treatment also increase glucose tolerance, like that of ranitidine, but the effect was less pronounced, given rise to a peak serum glucose level after 1.5 hr from glucose loading amounted to 139.5 mg% , 129.9 mg% and 119.4 mg%, respectively for half, daily and double daily human therapeutic dose (1200 mg) as compared with control value 144.37 mg% with 2 P<0.001.

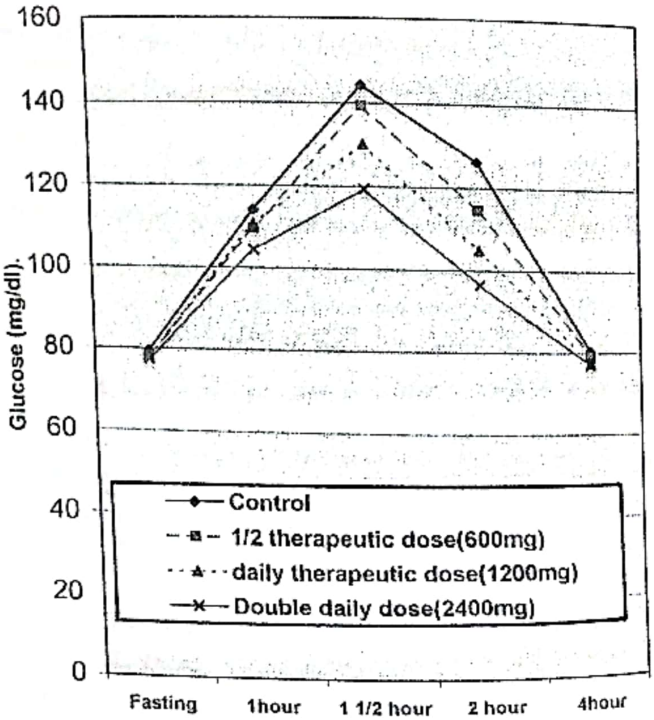

Fig.(2): Glucose tolerance curves after therapeutic doses of cimetidine for adult male albino rats (n= 10 rats).

As can be seen from Table (1), rats with gastrointestinal ulcer treated with ranitidine, revealed significant reduction in serum glucose level during three months of medication, the reduction were more pronounced with rising treatment dose from half to daily to double human daily therapeutic dose, exceeding values amounted to -22.18 mg% , -49.14mg% and -53.42mg% with P<0.0005 at the end of three months medication as compared with post-ulceration serum glucose level.

As displayed in Table (2) cimetidine produces a common reduction in magnitude of serum glucose during treatment period using the same doses schedule in case of ranitidine, but it exerted less potent reduction amounted to -15.60 mg%, -38.79 mg% and -48.14 mg% at the end of three months medication with P<0.005 as compared with its post-ulceration value.

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Table (1) : Effect of therapeutic doses of runtidine on glucose level of rats subjected to peptic ulcer by indomethathine.

Dose of treatment	Mean value for serum glucose ±S.E during lapse of time in month			
	After ulcer induction	1st month	2nd month	3rd month
½ daily therapeutic dose (150 mg)	121.818 ± 1.387	** 97.770±1.802	*** 97.478±0.909	*** 94.795±0.987
daily therapeutic dose (300mg)		** 78.154±1.266	*** 69.758±0.902	*** 61.961±0.553
Double daily dose (600 mg)		*** 69.755±1.106	*** 64.972±1.124	*** 56.733±.0.739

(n= 10 rats) Initial values = 77.187 ± 0.970.

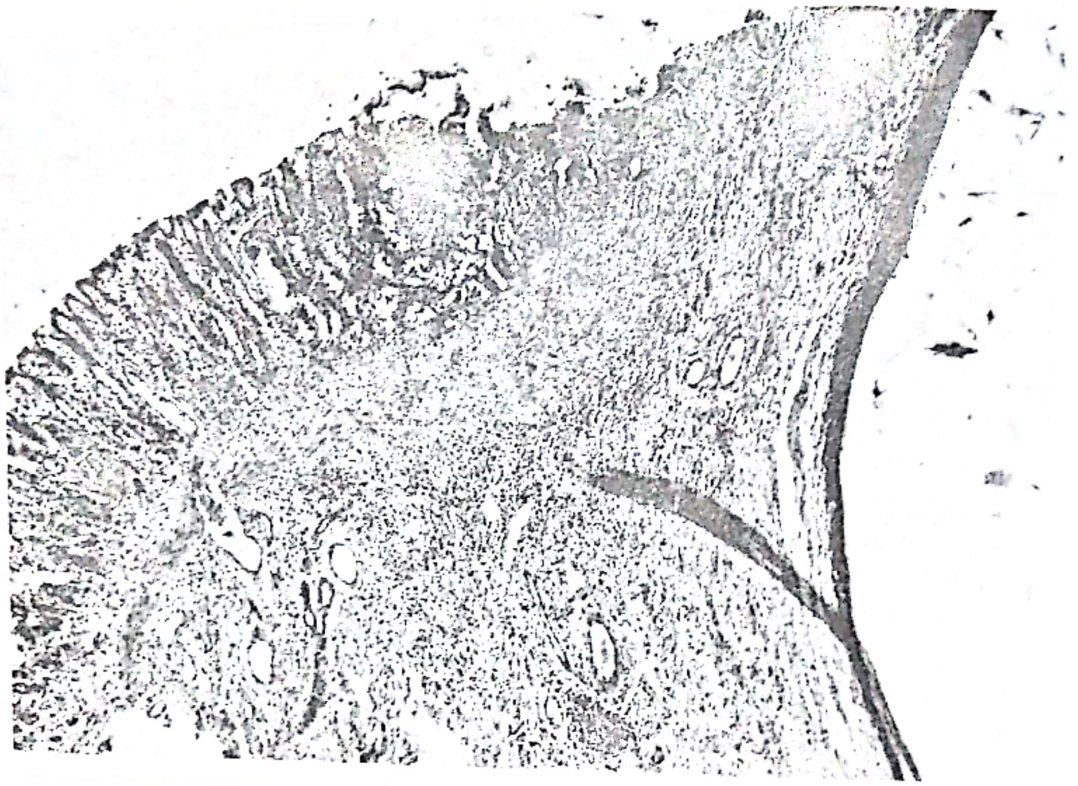
* P < 0.05 ** P< 0.005 *** P< 0.0001

Table (2) : Effect of therapeutic doses of cimetidine on glucose level of rats subjected to peptic ulcer by indomethathine.

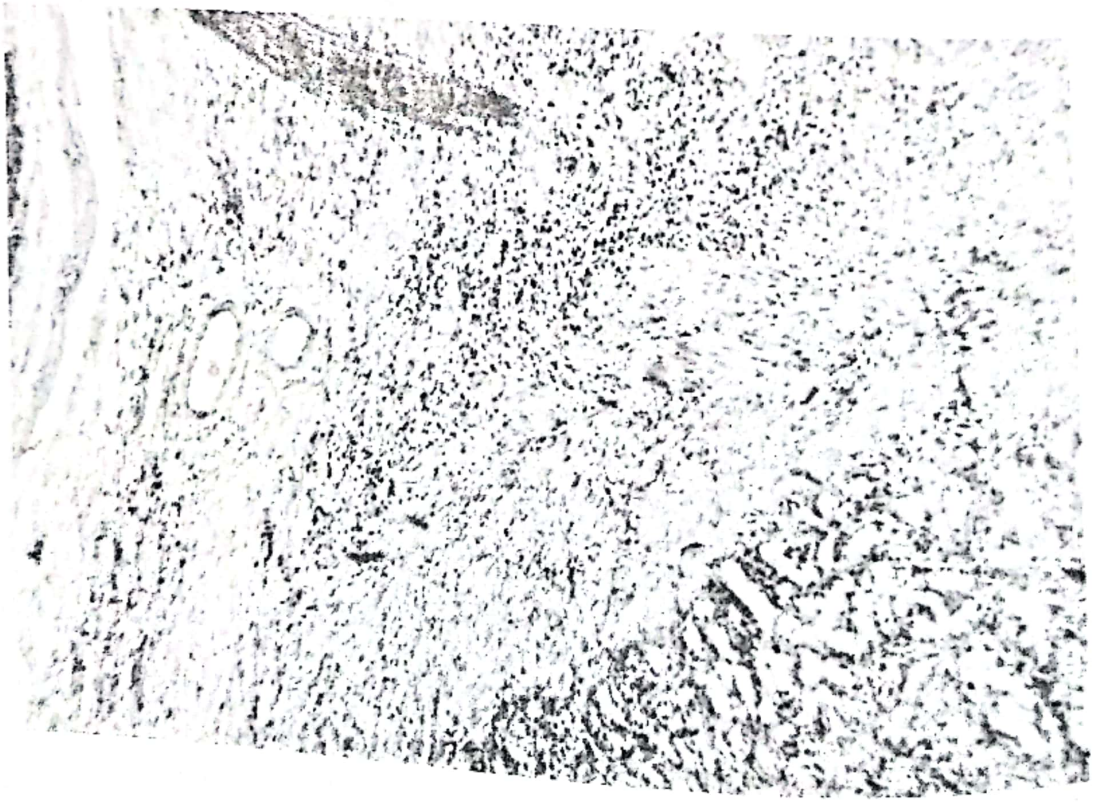
Dose of treatment	mg % of glucose mean value ± S.E during lapse of time in month			
	After ulcer induction	1st month	2nd month	3rd month
½ daily therapeutic dose (600 mg)	117.636± 1.169	*** 98.960±1.217	99.860±0.527	*** 99.320±0.527
daily therapeutic dose (1200mg)		*** 85.698±0.945	*** 78.605±0.997	*** 72.006±1.104
Double daily dose (2400 mg)		*** 74.910±1.143	* 65.966±1.145	** 61.009±.0.591

(n= 10 rats) Initial values = 77.187 ± 0.970.

* P < 0.05 ** P< 0.005 *** P< 0.0001



(A) (H. & E. X 40)



(B) (H. & E. X 100)

Fig. 3 : (A & B) : Gastro esophageal junction show discontinuity of the lining gastric mucosa, with area of fibrotic , changes , scattered and focal collection of mononuclear inflammatory cells. Small fragment of the lining esophageal mucosa is rean showing mild atypia .

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DISCUSSION

The ability of the body to utilize carbohydrate may be ascertained by measuring its glucose tolerance It is indicated by the nature of the blood glucose curve following the administration of amount of glucose [9].

Our intention in the present investigation was to clarify the role of different doses of ranitidine and cimetidine (histamine H_2 -receptor antagonist) on glucose tolerance in normal and gastrointestinal ulcer rat model .

As presented from our results the marked increase in glucose tolerance were parallel to increasing doses of both drugs, this means that glucose tolerance was dose dependent of histamine H_2 -receptor antagonist drugs. This finding may be explained , due to the effect of both drugs in stimulation of insulin secretion from β- cells of the pancreas, in manner to increase tolerance to carbohydrate [10] . This explanation was not in good keeping with the study done by, **Chariot et al.,** [11] in which they studied the effect of H_2 - receptor antagonist ranitidine on pancreatic exocrine secretion in rat, using cimetidine as a reference. They found that ranitidine, did not change basal hormonal secretion. On contrast, cimetidine, inhibited pancreatic response to glucose load. The different behaviour of the two H_2- antagonists suggests that the effect of ranitidine is independent of H_2 -receptor blockade and most probably connected with cholinergic - like action of drug .

Also the increase in glucose tolerance due to cimetidine or ranitidine doses treatment may be due to their action in stimulating hepatic clearance of glucose [12] .

Czyzyk et al[13] reported that hypoglycemia following alcohol ingestion significantly enhanced by all H_2- receptor antagonists and not dependent on the increase of ethanol absorption from gastrointestinal tract but represents rather specific effect of these drugs on glucose metabolism.

Increased tolerance to glucose is observed in pituitary or adrenocartical insufficiency and attributable to decrease the antagonism to insulin by hormones normally secreted by these glands [10] . Thus the observed reduction in serum glucose due to both drugs medication in rats with gastrointestinal ulcer presented in this study , proved that both drugs may act to antagonize the action of pituitary or adrenal cortex hormones, which inhibit the utilization of glucose in extrahepatic tissues through their action in antagonistic insulin, [9] , or may interpreted by the action of these drugs on inhibition the secretion of glucagon from α-cells which in turn reduce glycogenolysis and gluconeogenesis.

Feely et al. [14] , proved that both cimetidine and ranitidine caused a significant reduction in the postparandial rise blood glucose, though according to our finding that cimetidine and ranitidine reduce serum glucose level. We concluded that, careful attention should be taken before treatment with these drugs espccially people with lower blood glucose and diabetic patients suffering from gastric ulcers.

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تقدير التأثير المتحمل لجرعات سيمتيد من ورانتدين على الإ ستفادة من الجلوكوز فى الجرذان الطبيعية والجرذان المستحدث بها قرحة

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حيث أن قدرة الجسم على الإستفادة من الجلكوز يمكن تحقيقها عن طريق قياس تحمل الجسم للجلكوز لذلك فى هذه الدراسة تم تكريس الجهد لدراسة تأثير جرعات علاجية مختلفة من الأدوية المستخدمة فى علاج قرحة الجهاز الهضمى مثل سيمتيدين ورانتدين وذلك على مدى الإستفادة من الجلكوز فى الجرذان الطبيعية والجرذان التى إستحدث قرحة للجهاز الهضمى بها.

وقد استخدمت فى هذه الدراسة مجموعتان من ذكور الجرذان السويسرية أعطيت المجموعة الأولى فيها ثلاث جرعات مختلفة من سيمتدين عن طريق الفم وهى (٤٥مجم /كجم و ١٠٨ محم /كجم و٢١٦ مجم / كجم) وكذلك أعطيت المجموعة الثانية ثلاث جرعات عن طريق الفم من دواء رانتدين (٥ر١٣ مجم/ كجم و ٢٧مجم/كجم و ٤٥ مجم /كجم) وهى على التوالى تعادل نصف الجرعة والجرعة والجرعة الكاملة والجرعة المضاعفة للجرعة العلاجية اليومية التى يتعطاها الإنسان .

ولقد استخدمت كل مجموعة من الجرذان كمجموعة ضابطة لنفسها - وتم أعطاؤها الجرعات الثلاث لنفس المجموعة على ثلاث مراحل متتابعة بعد فترة سماح اسبوعية بين كل جرعة وأخرى. ولقد تم تعاطى الجرعات بساعة واحده قبل تعاطى الحيوانات لجرعة من الجلوكوز تعادل ١ جم / كجم من وزن الجسم.

وأوضحت النتائج المستحصل عليها من عينات متكررة (بعد ١ و ٥ر١ و ٢ و ٤ ساعات) من تعاطى الجلوكوز ثم تم تعيين نسبة الجلوكوز بها عن زيادة فى تحمل الجسم للجلوكوز وذلك بزيادة الجرعات العلاجية بالنسبة لكل من السيمتيدين و الرانتدين أما فى حالة مجموعة الجرذان التى تم استحداث قرحة بجهازها الهضمى وذلك عن طريق تعاطى ١٠مجم/كجم من عقار إندومثياسين عن طريق الفم لمدة خمسة أيام متتالية ثم تم معالجتهم على مدى ثلاثة أشهر بواسطة الأدوية السابقة وقد أثبتت النتائج وجود نقص معنوى واضح شهرياً بالنسبة للجلوكوز فى مصل الجرذان وقد لوحظ أن هذا النقص متماشياً طردياً مع زيادة الجرعات العلاجية لكلا العقارين .

ونستخلص من النتائج السابقة أنه يجب توخى الحذر قبل المعالجة بهذه العقاقير خاصة للمرضى ذوى مستوى السكر منخفض في الدم ولمرضى السكر الذين يعانون من قرحة فى المعدة.