INTRODUCTION

Diabetes mellitus is a metabolic disease caused by either impairment of pancreatic insulin secretion or impaired tissue responsiveness to insulin or through both ways(1). The dysfunction of pancreatic β-cells may be due to invasion by viruses, chemicals, toxins or autoimmune antibodies (2). This metabolic disease affects diverse organs of the body systems producing its long-term complications such as micro- and macro-angiopathies, atherosclerosis, congestive heart failure, hypertension, diarrhoea and spontaneous abortion (3) and neuropathy (4, 5). Most diabetic patients with prolonged exposure to this disease are prone to gastrointestinal disturbances such as bacteria overgrowth - induced diarrhoea and gastroparesis (6). These complications, most times engender multidrug therapy that when not properly administered and monitored may lead to adverse drug interactions.

Gastrointestinal disorders in diabetic patients most times, warrant the co-administration of the imidazole drugs (metronidazole and cimetidine) and sulphonylureas, the primary oral hypoglycemic drugs used in the management of diabetes. These imidazole drugs are known to inhibit certain enzymes responsible for the metabolism of some drugs thereby prolonging the

PHARMACODYNAMIC EFFECTS OF CIMETIDINE AND METRONIDAZOLE ON THE BLOOD GLUCOSE LOWERING EFFECT OF GLYBURIDE IN RATS.

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ABSTRACT

The effects of the two imidazole derivatives (cimetidine and metronidazole) on the control of blood glucose level by Glyburide were determined in normal and hyperglycemic rats. Both imidazole derivatives insignificantly reduced the blood glucose lowering ability of glyburide in both normal and hyperglycemic rats after a single dose administration. However, on the chronic administrations for 3 weeks, there were no observed significant variations in blood glucose levels of all the treated rats. Although the drugs did not significantly affect the control of blood glucose levels by glyburide, precautions must be taken when the need to co-administer these drugs arises especially in a prolonged therapy situation.

Keywords: Glucose lowering, normoglycemic, hyperglycemic, imidazole derivatives and Glyburide
pharmacological effects of these drugs in
the patient (7) and may affect the
pharmacokinetics of such drugs (8).
Glyburide is metabolized in the liver by
cytochrome P$_{450}$ enzymes, which are
often times inhibited by the imidazole
drugs, cimetidine and metronidazole (9).
Glyburide, a potent oral hypoglycemic
agent, can precipitate severe hypoglycemia when its action is
prolonged by enzyme inhibition. These
agents that can inhibit the metabolism of
glyburide to inactive metabolites could
lead to its adverse effect – hypoglycemia.
Although most diabetic patients suffering
from gastrointestinal tract disorders and
infectious diarrhoea are often treated with
metronidazole or cimetidine concurrently
with oral hypoglycemic agents, no
documented study on their
pharmacodynamic interactions has been
reported in recent literature. This study
therefore has been designed to
understudy the pharmacodynamic effects
of these imidazole drugs on the control of
blood glucose level by glyburide, using
animal model.

MATERIALS

Drugs
Glyburide, 5 mg (Daonil® , NGC,
Nigeria) tablets were weighed, crushed
and dissolved in Tween-20 to give 5
mg/ml. Cimetidine 200 mg tablets
(Cemtab® Fidson, Nigeria) and
Metronidazole (Amebanil® Dana,
Nigeria) 200 mg were similarly treated.
All drugs were administered immediately
after dissolution to avoid degradation.
Alloxan monohydrate (Sigma, USA) was
administered 120 mg/kg body weight
intraperitoneally (ip).

Animals
White albino rats of both sexes (120-150
g body weight) bred and housed in the
animal house of the Department of
Pharmacology and Toxicology,
University of Nigeria, Nsukka were used.
The animals were kept to acclimatize
with laboratory condition for 7 days with
free access to water and food before the
experiments.

Effects of cimetidine and
metronidazole on the control of
blood glucose level by glyburide in
normal rats

Twelve albino rats of 120-150 g
body weights were fasted for 12 h.
Blood sample was withdrawn from
the tail vein of the rats and blood
glucose level determined using the
One Touch Glucose Meter
(Lifescan® USA).
The rats were divided into 3 groups of
four rats per group. Group 1 received 5
mg/kg of Glyburide only; group 2
received 25 mg/kg Cimetidine and 5
mg/kg glyburide, while group 3 received
25 mg/kg metronidazole and 5 mg/kg
glyburide. The cimetidine and
metronidazole were orally administered,
30 minutes before the administration of
glyburide. Blood samples were collected
at 0, 1, 2, 4 and 8 hr from the rats and
blood glucose levels determined using
One-Touch Glucose meter kit.

Effects of Cimetidine and
Metronidazole on the control of
blood glucose level by glyburide in
alloxanized rats

Twelve albino rats of 120-150 g body
weight of both sexes were used. The rats
were made hyperglycemic by injecting
alloxan monohydrate (120 mg/kg)
intraperitoneally. The rats were fed for 8
days but on day 9, they were fasted for 12
hr and their blood glucose levels determined. The animals with blood glucose levels above 160 mg/dl were grouped into three of four animals per group and dosed as in the normoglycemic animal experiment on day 9. The blood samples were collected at intervals of 0, 1, 2, 4 and 8 h and blood glucose levels determined as before. The collections were continued at weekly interval for 3 weeks according to the method described by Okonta (1).

**Statistical analysis**

Mean blood glucose levels were expressed as mean ± SEM, and the significance of difference between the blood glucose levels at zero time and other time intervals in each treatment group determined using student’s t-test (p=0.05) and ANOVA to compare the various groups.

**RESULTS**

From the effect of the different imidazole derivatives (cimetidine and metronidazole) on the control of mean fasting blood glucose levels of both normoglycemic and hyperglycemic rats by glyburide, the glyburide –cimetidine combination caused 15.6% and 61.6% respectively, and glyburide – metronidazole combination caused 16.1% and 65.7% respectively on normoglycemic and hyperglycemic rats.

From the results, the effects of the combinations on the normoglycemic rats were insignificant (Table 1).

In hyperglycemic rats, glyburide-cimetidine and glyburide –metronidazole combinations lowered the mean fasting blood glucose levels from 196.6±18.3 mg/dl (0h) to 75.5±20.1 mg/dl (4 h) and 220±36.0 mg/dl (0 h) to 41.02±1.54 mg/dl (8 h) respectively. These combinations caused lower percentage maximal reduction of mean fasting blood glucose level than Glyburide alone though the percentage maximal reductions were not statistically significant (Table 2).

From Fig.1, the chronic administration of the glyburide –cimetidine and glyburide-metronidazole for 3 weeks showed no significant difference in the mean fasting blood glucose level at the 21st day from that of glyburide alone.

**DISCUSSION**

Glyburide is a potent oral hypoglycemic agent that lowers blood glucose level through pancreatic and extra pancreatic ways especially in hyperglycemic patients with partially viable beta cells (10, 11). In the normoglycemic rats, the beta cells were viable but the percentage maximal reduction of blood glucose level caused by glyburide was not significantly altered by co administration of glyburide and the imidazole derivatives –cimetidine and metronidazole. In the alloxanized rats however, glyburide alone caused significant percentage maximal reduction in blood glucose level while the co administration of glyburide with cimetidine and metronidazole did not enhance the percentage maximal reduction of blood glucose level by glyburide. These findings corroborate the findings of Kubacka and associates( 12) who observed that the co administration of H2-receptor antagonists, cimetidine and ranitidine, and glibenclamide led to unexpected higher plasma glucose levels than the sulphonylurea alone; and plasma insulin concentrations were significantly elevated when H2- receptor antagonists and glibenclamide were administered concurrently. The effects of the H2-
receptor antagonists and metronidazole on the blood glucose lowering activity of glyburide may be particularly resident on the imidazole moiety since all the imidazole derivatives co-administered with glyburide caused increase in plasma glucose levels although not significantly different from that of glyburide alone.

Glyburide metabolism is dominantly influenced by cytochrome CYP2C9 (13). Cimetidine and other imidazole derivatives are known to be 2C9 cytochrome isoform inhibitors hence could inhibit the glyburide metabolism and cause its prolonged hypoglycemic action. In our present study however, the reverse seems to be the case as the co-administration of these imidazole derivatives caused less reduction of the maximal percentage reduction of blood glucose level compared to that caused by glyburide.

### TABLE 1: Effects of Cimetidine and Metronidazole on glyburide treated normoglycemic rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean fasting blood sugar level (mg/dl) (MFBSL)</th>
<th>% Max. Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107.0±10.85</td>
<td>45.6±3.05</td>
</tr>
<tr>
<td>2</td>
<td>86.6±5.14</td>
<td>54.0±1.09</td>
</tr>
<tr>
<td>3</td>
<td>60.0±5.62</td>
<td>47.1±2.84</td>
</tr>
</tbody>
</table>

Grp. 1. Glyburide (5 mg/kg); Grp. 2. Glyburide (5 mg/kg) + cimetidine (25 mg/kg); Grp. 3. Glyburide (5 mg/kg) + metronidazole (25 mg/kg). Values are expressed as mean ± SEM; n=4

### TABLE 2: Effect of Cimetidine and Metronidazole on glyburide treated hyperglycemic rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean fasting blood sugar level (mg/dl) (MFBSL)</th>
<th>% Max. Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108.5±41.3</td>
<td>113±46.7</td>
</tr>
<tr>
<td>2</td>
<td>142.3±38.9</td>
<td>109.0±58.7*</td>
</tr>
<tr>
<td>3</td>
<td>91.3±20.7*</td>
<td>90.3±33.3*</td>
</tr>
</tbody>
</table>

Grp. 1 Glyburide (5 mg/kg); Grp. 2 Glyburide (5 mg/kg) + cimetidine (25 mg/kg); Grp. 3 Glyburide (5 mg/kg) + metronidazole (25 mg/kg). Values are expressed as mean ± SEM; n=4

*P<0.05 vs. 0 h
Although the hypoglycemic effect of glyburide may not be significantly affected by cimetidine and metronidazole co-administration as indicated in this study, precaution must be taken on individual basis when the need to co-administer these combinations arises.

REFERENCES


Fig. 1: Effects of chronic administration of cimetidine and metronidazole on blood glucose lowering effect of glyburide in hyperglycemic rats

1. **INTRODUCTION**

- Glyburide, 5mg/kg
- Glyburide, 5mg/kg + cimetidine, 25mg/kg
- Glyburide, 5mg/kg + metronidazole, 25mg/kg