Hypoglycemic and antihyperglycemic effects of newly synthesized sulfonyloxy derivatives of azalactone in normal and alloxan diabetic rabbits

Type-2 diabetes (noninsulin-dependent diabetes mellitus or NIDDM) is a major health problem because of its high frequency, long duration and high risk of chronic complications. At present sulfonylureas (II and III) generation,[1,2] biguanides, α-glucosidase inhibitors and thiazolidinediones are the pharmacological agents used orally in the management of this condition. However, their use causes variable incidence and range of untoward effects, such as skin rashes, dilutional hyponatremia, transient leucocytopenia, thrombocytopenia, myocarditis, severe hypoglycemia, increased chances of cardiovascular deaths of unknown mechanism, lethal lactic acidosis (rare), weight loss or weight gain and edema. This highlights the importance for alternative drugs having insulinotropic effects with minimal and tolerable adverse effects.

In order to improve the therapeutic variety, we have synthesized sulfonyloxy derivatives of azalactone, sulfonyloxy compounds have close structural resemblance to sulfonylureas and compounds bearing sulfonyl group (sulfonylureas, sulfonamides, etc.) have shown eminence biological activities.[1,2] However, these compounds have not been studied extensively. The synthesis and structure elucidation[3] of these compounds were reported earlier.[3] In the present study, derivatives of these compounds having the structure given below were tested for their acute antihyperglycemic and hypoglycemic activity in alloxan-induced diabetic and normal fasted rabbits, respectively.

The solutions of compounds were prepared in polyethylene glycol (P.E.G.400) to get a concentration of 40 mg/ml. Glibenclamide 2% suspension was prepared using gum acacia. Albino rabbits of either sex (1-2-kg) were selected as test

### Table 1

Effect of MTDA, MNADA and OCADA on blood sugar levels in normal and alloxan diabetic rabbits

<table>
<thead>
<tr>
<th>Group</th>
<th>Groups</th>
<th>Dose mg/kg</th>
<th>Blood glucose level in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal rabbits</td>
</tr>
<tr>
<td>I</td>
<td>Control</td>
<td>5 ml (PEG 400)</td>
<td>92.30 ± 5.11</td>
</tr>
<tr>
<td>II</td>
<td>MTDA</td>
<td>100</td>
<td>84.91 ± 5.61</td>
</tr>
<tr>
<td>III</td>
<td>MNADA</td>
<td>100</td>
<td>91.44 ± 6.09</td>
</tr>
<tr>
<td>IV</td>
<td>OCADA</td>
<td>100</td>
<td>87.45 ± 3.40</td>
</tr>
<tr>
<td>V</td>
<td>Glibenclamide</td>
<td>0.25</td>
<td>89.95 ± 2.30</td>
</tr>
</tbody>
</table>

One-way ANOVA: F = 58.99, df = 4, 25, P < 0.001

%change was calculated using formula %change = [(Tf-T0)/Tc]x100 where in Tc values of Before administration of drug, Tf values of after administration of drug. *P < 0.001 (Dunnett’s test); Data are expressed as mean ± SD, n=6 in each group.
animals. They were fed pellet food (Chakan Oil mills, Pune),
green vegetables, soaked grams and water ad libitum and
maintained under standard laboratory conditions (temperature
24-28°C, relative humidity 60-70%). Fasted rabbits were
derived of food for 16 hours but had free access of water.
Rabbits were made diabetic by injecting alloxan monohydrate
(1 mg/kg) intravenously in the marginal vein of ear at a dose of
200-250 mg/dl were considered as diabetic and
included for the study.

The normal fasted rabbits and diabetic rabbits were divided
into five groups of six each. Group-I served as control and
received the vehicle (P.E.G. 400). Groups II–V received the
solutions of newly synthesized compounds MTD, MNAD, NOCA
at a dose of 100 mg/kg and glibenclamide suspension
orally, respectively. Blood samples were collected
from the marginal ear vein at 0, 1, 3, 5, 7, 24 and 48 hours
after the administration of drugs.

Blood glucose level was estimated by autoanalyser (Make
- Transasia, Erbachem-5, Bombay) using the commercial
enzyme estimation kit (Monozyme India limited, Secundrabad,
Mumbai).

The results are expressed as mean ± S.D. The difference
between the groups was determined using the one way analysis
of variance (ANOVA) followed by Dunnett’s test with 5%
significance level (P<0.05). [7],[8]

The vehicle (P.E.G. 400) did not produce any significant
alteration in blood glucose level. All the compounds produced
significant hypoglycemic and antihyperglycemic effect and peak
effects were observed at an interval of 5 hours (Table-I).

MTD produced comparatively less hypoglycemic
(17.39±4.61%) and antihyperglycemic (18.37±5.29%)
peaks as compared to that produced by glibenclamide (i.e.
39.95%±3.43% and 38.55%±4.92%, respectively). However,
compounds MNAD and NOCA produced somewhat
equipotent hypoglycemic and antihyperglycemic peak effects
to that produced by glibenclamide. [Table 1]

The study reports for the first time the hypoglycemic and
antihyperglycemic effects of sulfonyloxy derivatives of
azalactone. The compound MTD (m-toluidine derivative
of azalactone) showed little fall in blood glucose levels, where as
compound MNAD (m-nitroaniline derivative of azalactone)
and NOCA (o-chloroaniline derivative of azalactone) produced
significant hypoglycemic as well as antihyperglycemic effects
in normal and alloxan-induced diabetic rabbits.

It is evident from the study that compounds MNAD and
NOCA have similar antihyperglycemic and hypoglycemic effects.
The data suggest that compounds MNAD and NOCA
could have therapeutic usefulness in diabetes mellitus.

Studies are in progress to elucidate in detail the mechanism
of action of these compounds at cellular and molecular levels
and their toxic effects.

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