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Original article

Evaluation of diphenhydramine in talc induced type 2 diabetes mellitus in Wistar rats

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ABSTRACT

Evaluation of diphenhydramine in talc induced type 2 diabetes mellitus was done in Wistar rats. Oral administration of Talc (10 mg/kg)carried out for 21 days increased the levels of serum glutamate pyruvate transaminase (SGPT), glutamate oxaloacetate transaminase (SGOT), serum creatinine, blood glucose, urea, uric acid and triglycerides (TGs), but when the animals were treated with diphenhydramine (DPH), the levels of the aforementioned biochemical parameters decreased significantly ($p < 0.0001$). The level of serum cholesterol and high density lipoprotein (HDL) was found to be reduced in Diabetes Mellitus (DM) control and when it was treated with DPH control animals, these makers increased significantly. The study done on DM and Diphenhydramine suggests that Talc increases the blood glucose level at a dose of 10 mg/kg (0.14 gm) and Diphenhydramine (1 mg/kg)reduces the increased blood glucose level. These finding simply that diphenhydramine may be useful in the management of talc induced diabetes.

1. Introduction

Diabetes Mellitus is a metabolic disorder which affects secretion of insulin as well as activity of insulin [1]. Deficiency of insulin ultimately creates chronic hyperglycemicstate and abnormal metabolism of protein, fat and carbohydrate [1]. As the diabetes progresses vascular or tissue damage may occur which finally can give rise to several complications associated with diabetes like neuropathy [2], retinopathy, [3,4] nephropathy [5], cardiovascular complications [6] and ulceration [7]. Diabetes is also the root cause of several heterogeneous diseases. In 2015, there were more than 415million people in the world suffering from diabetes 2 and it is estimated that by 2040 around 642 million people will suffer from it [8]. The latest recommendations on diagnosis and treatment of diabetes was published by the American Diabetes Association in August 2017 and by the WHO in July 2017. Potential mechanisms have been suggested for Talc and Diphenhydramine for induction and suppression of diabetes.Talc is a powdered form of hydrated magnesium silicate. The formula of pure talc is $[Mg_3Si_4O_{10}(OH)_2$ and its Molecular weight is 379.3 [9]. Mg^{2+} ions play an important role in glycolytic pathway. Phosphorylation is an essential step in the enzymatic conservation of metabolic energy so that the phosphorylated glycolytic intermediates cannot leave the cell. These glycolytic intermediates and phosphate groups form complex with Mg ion to become intact inside the cell [10]. Talc contains Mg silicate which is a complex or chelate form of Mg.This Mg silicate might compete with the Mg^{2+} ion forits binding site and may displace it inside the cell leading to disturbances in glycolytic pathway such that glucose may come out from the cell into the bloodstream leading to increased blood glucose level. But this mechanism is not clearly understood, further study on this is needed. It is well known fact that diphenhydramine reduces secretion and it may also inhibit the secretion of blood glucose from liver to blood Simesek et al., 2015. Sucraseisomaltase enzyme is found in the striated cell borders area small intestinal absorptive cells of the villus of human. Diphenhydramine inhibits sucrase enzyme in the intestine which convert sucrose in to glucose and fructose. Inhibition of sucrase enzyme can lead to control blood glucose level and hyperglycemia may be treated [11]. With these facts in sight, this study has been design to evaluate the effect of diphenhydramine on talc induced hyperglycemia.

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Table 1
Effect of Talc & DPH various pharmacological interventions on body weights, Creatinine, Urea and blood glucose of animals.

S. No.	Groups	Body weight (g)	Creatinine (mg/dl)	Blood glucose (mg/dl)	Urea (mg/dl)
1	Normal control	103.4 ± 5.562	0.6040 ± 0.05464	79.40 ± 5.492	33.80 ± 2.518
2	Diabetic Mellitus control (DM)	142.0 ± 23.17###	0.7940 ± 0.01778###	194.0 ± 9.482###	70.20 ± 1.908###
3	DPH control	108.7 ± 3.165***	0.6220 ± 0.04576***	100.6 ± 14.47***	37.20 ± 3.007***
4	DM + DPH control	109.2 ± 1.875***	0.5880 ± 0.03891***	130.6 ± 8.964**	48.80 ± 3.007***

Each Values in above table are expressed as Mean ± SEM, for each group (N = 5) where.
P < 0.001 Normal control Vs. DM control groups.
*** P < 0.001 DM control Vs. DPHC + DM group. ***P < 0.001 DMcontrol vs. DPHC groups.

2. Materials and methods

2.1. Drugs and chemicals

Diphenhydramine was obtained as a gift sample from Alben Chemical Pvt Ltd. (Mumbai); Talc was provided by Siddhartha Institute of Pharmacy and Diethyl ether and Chloroform from S.D. Fine Chem. Ltd. (Mumbai). All the chemicals used were of analytical grade quality.

2.2. Animals

Healthy, adult, male albino Wistar rats (100–125 g) were obtained from animal house, Siddhartha Institute of Pharmacy, Dehradun, India. The rats were randomly divided in four groups and kept in cages under standard temperature (22 ± 3 °C) and 14:10 h dark and light cycle and water and balanced pellet diet given *ad libitum*. The experimental work was approved by the Institutional Animal Ethical Committee*(Reference number SIP/IAEC/PCOL/08/2016)* in accordance with the guidelines of Control and Supervision of Experiments on Animals Committee, Siddhartha Institute of Pharmacy, Dehradun.

2.3. Induction of diabetes

Type 2 diabetes was induced by single administration of Talc (10 mg/kg body weight) [12] force feeding orally.

2.4. Experimental design

The animals were randomly segregated into four groups and every grouphad 5 rats: Group I animals were normal control and oral normal saline was given throughout experiment. Group II animals were given talc (10 mg/kg orally) for 21 days and served as Diabetes Mellitus Control (DM) group, Group III animals were administered with Diphenhydramine 1 mg/kg for 21 day after 21th day Talc 10 mg/kg was administered. Group IV rats were administered with Diphenhydramine as a control. The entire study was run for 42 days.

2.5. Biochemical parameters estimation

On the 42nd day of the study, the animals were sacrifices and blood sample was taken from the retro-orbital plexus under light anesthesia of ether and ketamine without anticoagulant and then allowed tost and at room temperature for 30 min then centrifuged for 10 min at 2500 rpm,and thus serum was obtained. The isolated serum was stored at 2–4 °C. The glucose level of blood was noted by digital glucometer (Abbott Diabetes care Inc, USA). A blood drop was put on a test strip of the glucometer. The level of glucose was shown within 20 s onto the screen. Serum SGPT, SGOT, TG, TC, TBR, HDL, urea blood glucose and uric acid was measured by using standard kits of Nicholas India Pvt. Ltd. with semi-auto analyzer (photometer 5010, Nicholas India Pvt. Ltd.).

2.6. Statistical analysis

All the results were shown as mean ± SEM. Statistical significance between more than two groups was tested using oneway ANOVA followed by the Bonferroni multiple comparison test or an unpaired two tailed student's *t*-test as appropriate using a computer based program (Graphpad Prism). Differences were considered to be statistically significant if $P < 0.0005$.

3. Results

3.1. Animal weight

DM control group showed significant increase in body weight as compared to normal control group animals. In Diphenhydramine control, the weight of body decreased in comparison to DM control. DM control + Diphenhydramine control group also showed significant reduction in the body weight as compare to DM control (Table 1).

3.2. Blood glucose

DM control group showed significant increase ($p < 0.0001$) in the level of blood glucose as compared to normal control. The level of blood glucose in the diphenhydramine control reduced significantly in comparison to DM control ($p < 0.0001$). DM control + Diphenhydramine control exhibited significant decrease ($p < 0.0001$) in the level of blood glucose as compared to DM control animal (Table 1).

3.3. Creatinine

In DM control rats, there was significant increase in serum creatinine level as compared to normal control ($p < 0.0001$). While in DPHC and DM + DPHC control the level was significantly decreased as compared to DM control ($p < 0.0001$) (Table 1).

3.4. Urea

Serum Urea level was found to increase ($p < 0.0001$) in DM control animals as compare to normal control and the level was reduced ($p < 0.0001$) when DM control animals were treated with Diphenhydramine. While in DPHC rats the urea level decreased significantly ($p < 0.0001$) as compared to DM control (Table 1).

3.5. Lipid profile

3.5.1. Total cholesterol

The levels of serum cholesterol decreased significantly ($p < 0.0001$) in DM control animal when treated with Diphenhydramine as compared to DM control. While the level increased in DM control rats when compared with normal control rats (Table 2).

3.5.2. Triglycerides (TGS)

TGS level increased ($p < 0.0001$) in DM control animals as