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## Effects of Oral Administration of Glucocorticoids, NSAIDs and Sulfonylureas on Blood Glucose in Mice

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**Abstract:** The research work was carried out to investigate the effects of oral administration of glucocorticoids (dexamethasone and prednisolone), NSAIDs (aspirin and paracetamol) and sulfonylureas (gliclazide and glibenclamide) on body weight and blood glucose in mice. Out of seven groups of mice (each containing 5 mice), one group was kept as control without giving any drug. Another six groups of mice received separately dexamethasone (Oradexon<sup>®</sup>, 3.5 mg kg<sup>-1</sup> b.wt.) prednisolone (Deltasone<sup>®</sup>, 8 mg kg<sup>-1</sup> b.wt.), aspirin (Ecospirin<sup>®</sup>, 620 mg kg<sup>-1</sup> b.wt.), paracetamol (Napa<sup>®</sup>, 333 mg kg<sup>-1</sup> b.wt.), gliclazide (Comprid<sup>®</sup>, 64 mg kg<sup>-1</sup> b.wt.) and glibenclamide (Glucotab<sup>®</sup>, 16 mg kg<sup>-1</sup> b.wt) orally along with normal feed. A significant ( $p < 0.05$ ) reduction of body weight was recorded on 7th day following administration of dexamethasone, gliclazide and glibenclamide in mice. This reduction was highly significant ( $p < 0.01$ ) on 21st, 42nd and 70th day following dexamethasone, gliclazide and glibenclamide treated groups. Similarly prednisolone significantly ( $p < 0.01$ ) reduced body weight of mice in whole experimental period. A significant ( $p < 0.01$ ) increase of the blood glucose level was found due to dexamethasone, prednisolone, aspirin and paracetamol administration on 7th, 21st, 42nd and 70th day. On the other hand, a significant ( $p < 0.01$ ) decrease of blood glucose level was found in mice treated with gliclazide and glibenclamide in whole experimental period. It may be concluded that oral administration of glucocorticoids, NSAIDs and sulfonylureas have variable effects on blood glucose level in mice.

**Key words:** Glucocorticoids, NSAIDs, sulfonylureas, blood glucose, mice

### INTRODUCTION

The first drugs which were recognized as providing a reliable and powerful anti-inflammatory effect were glucocorticoids. However, exogenous glucocorticoids administered at therapeutic level quickly bring an unpleasant and other dangerous side effect. Thus alternative means of controlling the various manifestations of the inflammatory process have been pursued. Current interest has been focused more on a group of drugs, which contains many diverse chemicals such as “nonsteroidal anti-inflammatory drugs”. The ability of the NSAIDs is to diminish the production of prostaglandin which acts as mediators of inflammatory response (e.g., pyrexia) and as modulators in pain perception<sup>[1]</sup>. NSAIDs are not free from toxic effects both in humans and livestock. The common clinical signs of toxicosis are vomiting, diarrhoea, CNS depression and circulatory dysfunctions<sup>[2]</sup>. The NSAIDs frequently cause irritation, bleeding and gastric ulcer. The major toxic effects included gastric ulcer, hepato-toxicity, impair platelet activity and analgesic nephropathy<sup>[3]</sup>. The other

side-effects associated with the use of NSAIDs include aseptic meningitis<sup>[4,5]</sup> and oral ulcerations<sup>[6]</sup>. The information on the effects of NSAIDs in most animals is limited. But the use of NSAIDs has been increasing with their greater effectiveness against fever, pain and inflammation.

Glucocorticoids are among the most widely used and misused class of drugs in Veterinary Medicine. Despite this, scientific information on glucocorticoids therapy in most domestic species is scarce, particularly with respect to optimal dosages and dosage intervals, physical and endocrine side effects and efficacy in clinical applications<sup>[7]</sup>. Much has been adopted from clinical use in humans and much more is known about the fine points of glucocorticoids therapy in dogs and cats than in other species. Because of their wide-ranging and non-specific effects, reports of the clinical use of glucocorticoids are replete with pragmatic recommendations regarding dosage, duration of therapy and severity of side effects. The effects of glucocorticoids are numerous and widespread as alteration in carbohydrate, protein and lipid metabolisms, preservation of normal function of the

cardiovascular system, immune system, skeletal system and endocrine system<sup>[8]</sup>. It is important to recognize that glucocorticoids rarely cure diseases, with the possible exception of spontaneous glucocorticoids deficiency. Glucocorticoids are used to try to suppress clinical signs long enough for a condition to run its natural course<sup>[9]</sup>.

The sulfonylureas were hypoglycemic sulphonamides which are capable of supporting life in diabetics with some functional  $\beta$ -cells, but are without effect in pancreatectomized animals<sup>[1]</sup>. Gliclazide and Glibenclamide are second generation of hypoglycemic sulfonylureas. Sulfonylureas causes hypoglycemia by stimulating insulin release from pancreatic  $\beta$ -cells<sup>[8]</sup>. The side-effects of sulfonylureas include nausea, vomiting, cholestatic jaundice, agranulocytosis, aplastic and haemolytic anaemia, generalized hypersensitivity reactions and dermatological reactions. So a wide knowledge about glucocorticoids, NSAIDs and sulfonylureas is indispensable for all. Of course, the present study is a preliminary work on blood glucose in laboratory animals in Bangladesh. The present work was undertaken to investigate the effects of different preparations of glucocorticoids, NSAIDs and sulfonylureas on body weight and blood glucose in mice.

#### MATERIALS AND METHODS

The experiment was conducted for a period of 70 days (1st August, 2001 to 9th October, 2001) in the Department of Pharmacology, Faculty of Veterinary Science, Bangladesh Agricultural University, Mymensingh, Bangladesh. Eight weeks old 35 male swiss albino mice (*Mus musculus*) were collected from International Centre for Diarrhoeal Diseases Research, Bangladesh (ICDDR), Mohakhali, Dhaka, Bangladesh. The mice in house were kept under close observation in order to acclimatize to the new environment for a period of one week prior to commencement of the experiment. All the mice were maintained under same environment such as similar animal house procedures like feeding, watering, bedding material replacement etc. Two glucocorticoids i.e. dexamethasone (Oradexon<sup>®</sup>, Organon Bangladesh Ltd.) and prednisolone (Deltason<sup>®</sup>, Renata Ltd., Bangladesh), NSAIDs drugs i.e. aspirin (Ecospirin<sup>®</sup>, The ACME Laboratories Limited, Bangladesh) and paracetamol (Napa<sup>®</sup>, Beximco Pharma. Ltd., Bangladesh) and sulfonylureas i.e. gliclazide (Comprid<sup>®</sup>, Square Pharma. Ltd., Bangladesh) and glibenclamide (Glucotab<sup>®</sup>, Fisons Bangladesh Ltd.) were used in the present study. The mice were divided into 7 equal groups containing 5 mice in each group. The groups were designated as group A, B, C, D, E, F and G of which group A kept as control.

Mice of group A were fed control diet or basal ration. Mice of group B, C, D, E, F and G were fed basal ration along with dexamethasone (3.5 mg kg<sup>-1</sup> b.wt.), prednisolone (8 mg kg<sup>-1</sup> b.wt.), aspirin (620 mg kg<sup>-1</sup> b.wt.), paracetamol (333 mg kg<sup>-1</sup> b.wt.), gliclazide (64 mg kg<sup>-1</sup> b.wt.) and glibenclamide (16 mg kg<sup>-1</sup> b.wt.), respectively. Body weight and blood glucose level were recorded on day 0 (pre-treatment) and on 7th, 21st, 42nd and 70th day of experimental period. Body weight was measured by the help of Electronic balance. Blood glucose level was determined with automatic Glucose meter (Glucotrend). A small drop of blood was collected directly from the tail of all mice and was placed on the glucose strips at Glucose meter.

The data were analyzed statistically by using student's 't' test<sup>[10]</sup> for the significance of differences in control and treated groups.

#### RESULTS AND DISCUSSION

The effects of oral administration of glucocorticoids (dexamethasone and prednisolone), NSAIDs (aspirin and paracetamol) and sulfonylureas (gliclazide and glibenclamide) on body weight of different groups of mice were represented in the Table 1. A significant ( $p < 0.05$ ) reduction of body weight was recorded on 7th day following administration of dexamethasone (3.5 mg kg<sup>-1</sup> b.wt.), gliclazide (64 mg kg<sup>-1</sup> b.wt.) and glibenclamide (16 mg kg<sup>-1</sup> b.wt.) in group B, F and G, respectively. This reduction was highly significant ( $p < 0.01$ ) on 21st, 42nd and 70th day following administration of dexamethasone, gliclazide and glibenclamide in group B, F and G. Oral administration of prednisolone (8 mg kg<sup>-1</sup> b.wt.) significantly ( $p < 0.01$ ) reduced body weight of mice in group C from 7th day onwards upto last day of experimental period (70 days). In accordance to these present findings Bray<sup>[11]</sup> reported that body weight was decreased in Japanese quail due to long term administration of dexamethasone. Similar response has been reported in rats by Kaur *et al.*<sup>[12]</sup> due to dexamethasone treatment. Knecht *et al.*<sup>[13]</sup> also reported similar findings by ingestion of prednisolone in Doberman Pinscher dogs. The decrease in body weight for glucocorticoids might be due to excessive catabolism, muscle atrophy and mobilization of free fatty acids from adipose store<sup>[7]</sup>. Shinzato *et al.*<sup>[14]</sup> reported that gliclazide increased body weight in rats. Similar response has been observed by Baynes *et al.*<sup>[15]</sup> due to glibenclamide treatment in men. The changes in body weight due to aspirin (620 mg kg<sup>-1</sup> b.wt.) and paracetamol (333 mg kg<sup>-1</sup> b.wt.) in group D and E, respectively were not statistically significant.

Table 1: The effects of oral administration of glucocorticoids (dexamethasone and prednisolone), NSAIDs (aspirin and paracetamol) and sulfonylureas (gliclazide and glibenclamide) on body weight (g) in mice

Groups of mice	Drug with dose (mg kg <sup>-1</sup> b.wt.)	Time in days				
		Pre-treatment	Post-treatment			
			0	7	21	42
A (control)	-	26.98±0.90	26.50±0.80	27.52±0.91	27.38±0.60	27.80±0.90
B	dexamethasone (3.5)	26.68±0.75	25.34±0.91*	25.10±0.86**	24.54±0.17**	22.66±0.55**
C	prednisolone (8.0)	26.48±0.52	23.22±0.74**	23.00±0.53**	23.84±0.66**	22.34±0.83**
D	aspirin (620)	26.60±0.50	26.80±0.50	26.80±0.37	27.00±0.48	27.10±0.31
E	paracetamol (333)	26.80±0.37	26.80±0.40	26.90±0.50	27.10±0.40	27.20±0.60
F	gliclazide (64)	27.40±0.41	28.70±0.12*	31.86±0.75**	32.26±0.22**	33.18±0.214**
G	glibenclamide (16)	24.58±0.80	25.26±0.40*	27.80±0.40**	29.74±0.70**	30.20±0.12**

The above values represent the mean ± standard error (SE) of 5 mice

\*\* = Significant at 1% level (P<0.01) \* = Significant at 5% level (P<0.05)

Table 2: The effects of oral administration of glucocorticoids (dexamethasone and prednisolone), NSAIDs (aspirin and paracetamol) and sulfonylureas (gliclazide and glibenclamide) on blood glucose level (mg/dl) in mice

Groups of mice	Drug with dose (mg kg <sup>-1</sup> b.wt.)	Time in days				
		Pre-treatment	Post-treatment			
			0	7	21	42
A (control)	-	8.10 ±0.05	8.10± 0.03	8.10±0.03	8.24±0.09	8.10±0.05
B	dexamethasone (3.5)	8.28±0.16	10.10±0.07**	11.12±0.09**	11.32±0.03**	11.33±0.03**
C	prednisolone (8.0)	8.10±0.04	10.50±0.07**	11.12±0.04**	11.26±0.14**	11.22±0.02**
D	aspirin (620)	8.24±0.10	8.52±0.07**	9.00±0.06**	9.54±0.12**	9.80±0.13**
E	paracetamol (333)	8.32±0.10	8.70±0.07**	9.12±0.12**	9.78±0.13**	10.16±0.14**
F	gliclazide (64)	8.28±0.33	6.64±0.72**	7.46±1.24**	6.60±1.59**	6.34±1.22**
G	glibenclamide (16)	8.12±0.31	7.12±0.58**	6.84±0.64**	6.70±0.84**	6.52±0.51**

The above values represent the mean ± standard error (SE) of 5 mice \*\* = Significant at 1% level (P<0.01)

The results of oral administration of glucocorticoids, NSAIDs and sulfonylureas on blood glucose level were shown in the Table 2. A significant (p<0.01) increase of the blood glucose level was found due to dexamethasone (3.5 mg kg<sup>-1</sup> b.wt.), prednisolone (8 mg kg<sup>-1</sup> b.wt.), aspirin (620 mg kg<sup>-1</sup> b.wt.) and paracetamol (333 mg kg<sup>-1</sup> b.wt.) administration in group B, C, D and E, respectively on 7th, 21st, 42nd and 70th day. In conformity to the present findings, Liang *et al.*<sup>[16]</sup> reported that dexamethasone increased blood glucose levels in broilers. Likewise, Furl and Knobloch<sup>[17]</sup> reported that prednisolone elevated the blood glucose levels in cows. Similar response has been reported by Kumar and Pachauri<sup>[18]</sup> due to prednisolone treatment in poultry. The increase of blood glucose level might be due to increase gluconeogenesis, decrease protein synthesis, reduce peripheral glucose utilization and activated lipolysis following glucocorticoids administration<sup>[7]</sup>. These results were agreeable with the findings of Bhaumik and Sharma<sup>[19]</sup> for paracetamol in sheep. The increase of blood glucose level might be due to NSAIDs increasing the output of glucocorticoids, displacing glucocorticoids from plasma-protein binding and increasing concentration of glucocorticoids. These glucocorticoids increase gluconeogenesis, decrease protein synthesis and reduce peripheral glucose utilization<sup>[1,7]</sup>. On the other hand, a significant (p<0.01) decrease of blood glucose level was found on day 7th,

21st, 42nd and 70th in group F and G treated with gliclazide (64 mg kg<sup>-1</sup> b.wt.) and glibenclamide (16 mg kg<sup>-1</sup> b.wt.), respectively. In confirmatory to the present findings, Chandra *et al.*<sup>[20]</sup> reported that glibenclamide lowered the blood glucose level in goats. Likewise, Elliot *et al.*<sup>[21]</sup> and Nelson *et al.*<sup>[22]</sup> reported that gliclazide therapy decreased the blood glucose level in cats. Similar response has been reported by Hotta *et al.*<sup>[23]</sup> due to sulfonylureas (gliclazide and glibenclamide) in man. The decrease of blood glucose level might be due to suppression of hepatic gluconeogenesis<sup>[24]</sup>. Adams<sup>[7]</sup> also noted that sulfonylureas therapy augments the ability of insulin to inhibit hepatic glucose production and to stimulate glucose utilization. It may be concluded that oral administration of glucocorticoids and NSAIDs increased the blood glucose but sulfonylureas decreased blood glucose in mice.

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