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Hyperglycemic Effect of High Doses of Diclofenac (Voltaren) in Rabbits

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SUMMARY

To study the effect of diclofenac (Voltaren) on blood sugar level in rabbits, various doses of the drug were given to various groups of rabbits and blood sugar level was checked after 1 hour, 3 hours, and 24 hours. A long-term study which was carried out on a group of rabbits in which the drug was given daily and blood sugar level was recorded after 1 week, 2 weeks, and 4 weeks. Laboratory of Fatima Jinnah Medical College, Lahore was used for a period of 1 year. Blood sugar level was estimated by using glucose kits GOD/PAP supplied by Randox Lab. Method was calorimetric method without deproteinization. The study showed that there was a significant increase in blood sugar level at 1 hour, 3 hours, and 24 hours interval after injection of various doses of diclofenac. The long-term study revealed that blood sugar level significantly increased after diclofenac. These results may be verified in a larger study and on humans.

INTRODUCTION

Rheumatic complaints are amongst the most common reasons for seeing a doctor especially in middle aged people. Millions of dollars worth of non steroidal anti-inflammatory drugs (NSAIDs) consequently being prescribed to fill an almost insatiable demand. Considerable number of the patients in this age group are suffering from mild moderate or severe diabetes or are prediabetic (latent diabetes).

Diclofenac or (Voltaren) is one of these NSAIDs which is quite popular now-a-days and is prescribed extensively in this age group. The present study is designed to see the hyperglycaemic effect of various of doses of Diclofenac in experimental animals (rabbits) in our study.

It will provide useful information and guide-line for correct choice in clinical use of this drug in patients who are prediabetic or suffering from diabetes, as hyperglycemic effects could worsen already existing diabetes or precipitate diabetes and be one of the factors for or poor response to antidiabetic drugs.

MATERIALS AND METHODS

Rabbits were weighed ranging from 0.6-1.1Kg. Six rabbits were used in each group. Blood sugar level was estimated by drawing 2ml of blood from the ear vein of the rabbit. Blood was centrifuged for about 10 minutes to 15 minutes at 4000 RPM and clear plasma was obtained. Blood sugar level was estimated by using glucose kits GOD/PAP[1].

The principle of the method is to determine glucose after enzymatic oxidation in the presence of glucose oxidase. The formed hydrogen peroxide reacts under catalysis of peroxidase with phenol and 4-aminophenazone to form a red-violet quinone-nine as indicator.

Reagents used from the supplied kit were:

1. Buffer solution
2. GOD-PAP reagent
3. Standard solution

A micropippete was used and 20μl of the plasma was put in all the tubes for blood sugar estimation. These were labelled as "tests". 2μl of the standard solution was put in one of the tubes and was labelled as "standard". One test tube was

labelled for blank. The 2ml or 2000μl of the prepared reagent was put in all the rest tubes *i.e.* those having sample, test, and blank labels.

Then they were mixed and incubated for 10 minutes at 37°C. The absorbance of the standard. (A standard) and sample, was measured against the reagent blank within 60 minutes. the wavelength selected was 546nm.

The calculations were done as follows:

$$mg\% = A\ sample \times \frac{100}{A\ standard}$$

Normal values were taken as 75-115mg%.

Readings were taken as follows:

For Short term Study

- **Group-I**

i. Normal blood sugar level was taken in this group of six rabbits and was taken as a control.
ii. Therapeutic dose of Diclofenac 1.07mg/Kg was then injected deep I/M.
iii. Blood samples were drawn after injection of the drug at an interval of 1 hour, 3 hours, and 24 hours.

- **Group-II**

In this group of six rabbits dose of the drug injected was double the therapeutic dose *i.e.* 2.14mg/Kg I/M. Sample for blood sugar estimations were taken at the same intervals *i.e.* 1 hour, 3 hours, and 24 hours.

- **Group-III**

In this group of six animals the dose of the drug injected was four times the therapeutic dose *i.e.* 4.28mg/kg I/M and blood sugar levels were determined at the same intervals *i.e.* after 1 hour, 3 hours and 24 hours.

For long-term study

- **Group-IV**

In this group of six rabbits, the dose selected was the third dose *i.e.* 4.28mg/Kg I/M. It was injected daily for a period of 4 weeks. Blood sugar level was determined at the end of every week for 4 weeks.

Statistical analysis

Statistical analysis of the results was done SD, SE and `*t*' test were calculated. If `*t*' value is greater than 2 results were significant.

RESULTS

In the first group a therapeutic dose of1.07mg/Kg of diclofenac was used. Mean blood sugar level before giving diclofenac was 100.89±2.23mg%. Blood sugar level after one hour of Inj. was 143.06±11.42mg%. Blood sugar after 3 hours of Inj. was 164.36±4.04mg%. Blood sugar level after 24 hours of Inj. was 135.33mg±8.39mg% (Table 1). All the results are highly significant ($p < 0.001$).

Table 1: First Group: Blood sugar level after I/M Inj. Diclofenac (1.07mg/Kg the therapeutic dose) (n=6).

Sr. No.	Weight of animal	Normal BSL (mg)	Dose	Blood sugar levels (in mg%) after 1 hr	3 hrs	24 hrs
1	0.6 Kg	106.15	Therapeutic	156.3	174.5	107.6
2	0.79 Kg	97.69	dose	114.09	172.7	118.09
3.	10.07 Kg	99.23		106.0	160.0	135.6
4.	1.07 Kg	93.84		180.0	153.0	155.14
5.	1.13 Kg	108.46		153.0.	172.0	160.6
6.	0.71 Kg	100.00		149.0	154.0	135.33
	MEAN	100.89		143.06	164.36	135.33
	SD	5.44		27.88	9.85	20.48
	SE	±2.23		±11.42	±4.04	±8.39
	t value			7.50	25.38	10.56
	P value			< 0.001	< 0.001	< 0.001

In the second group with double the therapeutic dose (2.14mg/kg), the mean blood sugar level before injection was 135.1±2.62mg%. Blood sugar levels one hour after diclofenac injection was 197.88±4.06mg%. Blood sugar level after 3 hours of Inj. was 186.93±7.43mg%. Blood sugar level after 24 hours of Inj. 172.5±6.71mg% (Table 2). All the results are highly significant ($P < 0.001$).

In the third group diclofenac was given in a dose of 4.28mg/kg *i.e.* four times the therapeutic dose. Mean blood sugar level before giving the Inj. was 97.06±0.29mg%. Blood sugar level 1 hour

after the Inj. of drug was 165.22±15.29mg%. Blood sugar level 3 hours after the Inj. of drug was 137.48±12.49mg%. Blood sugar level 24 hours after Inj. was 117.3±11.47mg% (Table 3). All he results are highly significant p<0.001.

Table 2: Second Group: Blood sugar level after I/M Inj. Diclofenac (2.14 mg/Kg double the therapeutic dose) (n=6).

Sr. No.	Weight of animal	Normal BSL (mg)	Dose	Blood sugar levels (in mg%) after 1 hr	3 hrs	24 hrs
1	1.19 Kg	132mg		211	135	164
2	0.68 Kg	107.5		177	184	223
3.	1.25 Kg	141.7	2.14	198.4	180	212
4.	1.36 Kg	140.6	mg/kg	188.7	154.9	130
5.	1.36 Kg	147.05		231.8	238.7	156
6.	1.36 Kg	142.1		180.39	229	150
	Mean	135.1		197.88	186.93	172.5
	SD	6.42		9.94	18.14	16.45
	SE	±2.62		±4.06	±7.43	±6.71
	t value			24.33	16.35	12.26
	P value			< 0.001	< 0.001	< 0.001

Table 3: Third Group: Blood sugar level after I/M Inj. Diclofenac (4.28mg/Kg 4 times the therapeutic dose) (n=6).

Sr. No.	Weight of animal	Normal BSL (mg)	Dose	Blood sugar levels (in mg%) after 1 hr	3 hrs	24 hrs
1	1.53 Kg	101.03	4.28mg	190.6	149.38	119.42
2	0.96 Kg	90.47	per Kg	180.15	130.2	110.68
3.	0.68 Kg	84		131.88	126.53	168.96
4.	0.90 Kg	103		123.69	162.04	117.93
5.	0.96 Kg	97.41		219.37	105.71	100.34
6.	0.79 Kg	106.45		145.67	151.02	86.53
	Mean	97.06		165.22	137.48	117.31
	SD	8.4		37.46	30.59	28.109
	SE	±0.291		±15.29	±12.49	±11.47
	t value			17.29	11.30	5.90
	P value			< 0.001	< 0.001	< 0.001

In the fourth group dose of drug was kept same as in 3rd group (*i.e.* 4.28mg/kg of diclofenac daily) Mean blood sugar level before Inj. was 97.06±0.291mg%. Blood sugar level at the end of first week was 195.88±28.99mg%. Blood sugar level at the end of second week was 172.46±28.66 mg%.

Blood sugar level at the end of 3rd week was 161.88±17.09mg%. Blood sugar level at the end of 4th week was 158.68±11.50mg% (Table 4). All the results are highly significant (P < 0.001).

Table 4: Fourth Group - Long term study: Blood sugar level after I/M Inj. Diclofenac (4.28 mg/Kg the therapeutic dose daily for 4 weeks (n=6).

Sr. No.	Wt. of animal (kg)	Normal BSL (mg)	Dose	Blood sugar levels (in mg%) after 1 wk	2 wks	3 wks	4 wks
1	1.53	101.03		100.0	103.22	112.23	122.84
2	0.96	90.47	4.28 mg	202.6	84.4	182.27	134.48
3.	0.68	84	per kg	154.22	198.38	227.42	166.37
4.	0.90	103		169.7	239.91	155.27	177.58
5.	0.96	94.41		299.1	155.24	169.62	151.72
6.	0.79	106.45		249.7	253.62	124.47	199.13
	Mean	97.06		195.88	172.46	161.88	158.68
	SD	8.4		71.00	70.219	41.66	28.18
	SE	±0.291		±28.99	±28.66	±17.09	±11.50
	t value	18.26		14.01	15.58	17.94	
	P value			<0.001	<0.001	<0.001	<0.001

DISCUSSION

Diclofenac (Voltaren) is a phenylacetic acid derivative that is a potent inhibitor of Cox (cyclo oxygenase). As such it possesses analgesic, anti-inflammatory and antipyretic effects. It is used in the treatment of rheumatoid arthritis, osteoarthritis as well as an ophthalmic preparation.

Although as a group, NSAID are remarkably safe to use but it has been demonstrated in man and animals that large doses of salicylates may induce hyperglycemia, glycosurea and deplete liver and muscle glycogen[1,2]. These effect may partly be explained by release of adrenaline. In these doses there is decrease in aerobic metabolism of glucose,

increase activity of glucose 6-PO_4 and increase secretion of glucocorticoid[3].

It has been reported by Prescot[4] that use of diclofenac may be associated with some increase risk of aplastic anaemic or impaired liver function; periodic tests for hepaic function are recommended.

Although in case of diclofenac sufficient literature is not available about its hyperglycemic effect but this experimental study strongly suggest that there is possibility of developing hyperglycemia in those patients with rheumatic complaints like rheumatoid arthritis, who are taking high doses of this analgesic for long durations. This preliminary animal study shows that there may be hyperglycemia associated with short-term and long-term use of diclofenac. This should be kept in mind when prescribing the drug.

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