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To study the effect of azoles (antifungal drugs) on blood glucose level in albino rabbits

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ABSTRACT

Background

Constant itching and inflammation due to fungal infection in a diabetic patient leads to stress, causing epinephrine to release which may cause change in blood glucose level mostly, results in hyperglycemia. Long term antifungal medication like azoles shows changes in blood glucose level which could be beneficial to diabetic patient. In the above context to see the probability, we conducted this study.

Aim

To study the effect of azoles (antifungal drugs) on blood glucose level in albino rabbits.

Material & method

Healthy male albino rabbits were taken and randomly distributed into groups and each group contain six rabbits(n=6). Rabbits in group I were treated with normal saline, group II rabbits were treated with insulin, group III rabbits with Glibenclamide, fourth group were treated with Fluconazole, Vth group with Itraconazole and group VI with Ketoconazole. Blood samples were collected before drug administration (0 hr.) and after administration of drug at 1hr, 2hr, 4th hr, 6th hr, and on 10th day. In case of insulin treated rabbits half an hour samples were also collected. The blood glucose levels were determined by GOD/POD method.

Result

Fluconazole and Itraconazole do not show any significant effect ($p > 0.05$) on blood glucose level in albino rabbits. While ketoconazole has insignificant effect ($p > 0.05$) on blood glucose level at one hour but significant effect at 2ndhr ($p < 0.001$) and 4th hr ($p < 0.001$). 6th hr blood glucose level is same as that of 1 hr ($p > 0.05$) and 10th day hypoglycemic effect (after 4 hr of drug administration) is almost similar to hypoglycemic effect observed by ketoconazole at 4th hr on 1st day. Ketoconazole induced hypoglycemia is approximately similar to Glibenclamide induced hypoglycemia at 2ndhr and 4thhr.

Conclusion

No significant effect with Fluconazole and Itraconazole but significant short term hypoglycemic effect with Ketoconazole. Watchful need should be taken in diabetic patient who are on hypoglycemic drugs.

Keywords: Azoles, Antifungal drugs, Diabetes mellitus, Albino rabbits, Fluconazole, Itraconazole, Ketoconazole, Insulin

INTRODUCTION

Fungal infections are not only common as primary disease but also common in patients suffering from diabetes mellitus. Due to fungal infections there is continuous itching & inflammation. They are known as chronic stressor and this chronic stress may change the normal blood glucose level by increasing the secretion of epinephrine which leads to decrease insulin secretion causing hyperglycemia and more chances of fungal infection. [1] Diabetic patient with fungal infection require antifungal as well as antidiabetic medication. Diabetes mellitus is one of the emerging problem and largest emerging threats to public health in 21st century. There is a greater frequency of metabolic disorder in diabetic patient. [2] Extra glucose in blood & urine increase the chances of many opportunistic infections and fungal infection is one of them. [3] Antifungal medication such as azole is effective to control fungal infection. Because fungal infection required therapy for longer duration and this is seen that antifungal drug shows alteration in blood glucose level. If any azole (antifungal) drug has capacity to reduce blood glucose level, it would be much beneficial to a diabetic individual suffering from fungal infection. To explore this possibility we see the effect of commonly used azoles (Fluconazole, Itraconazole, ketoconazole) on blood glucose level in albino rabbits.

MATERIAL & METHOD

This work was carried out in department of Pharmacology, GSVM Medical college, Kanpur. Healthy male albino rabbits weighing between 1-1.5kg were made available from animal house and were distributed randomly into 6 different groups. Each group contain 6 animals (n=6).The animal were kept under standard conditions as per the guidelines of CPCSEA. Prior approval was taken from institutional animal ethics committee (IAEC).

Drugs

- Group I-Animal of this group were treated with normal saline (Vision parenteral pvt.ltd) 0.5ml orally for 10 days.
- Group II -Animal of this group were treated with insulin (Wockhardt ltd) 1IU/kg subcutaneously.
- GroupIII- Animals of this group were treated with Glibenclamide (cadila health care pvt.ltd)0.05mg/kg/day orally for 10 days
- Group IV -Animal of this group were treated with Fluconazole (cipla ltd) 5mg/kg/day for 10 days
- Group V -Animal of this group were treated with Ketoconazole (torrent labs pvt.ltd)5mg/kg/day for 10 days
- Group VI -Animal of this group were treated with Itraconazole (systopic laboratories pvt.ltd) 5mg/kg/day for 10 days

Experimental protocol

Rabbits were fasted 10 hr prior to take blood samples. Samples were collected before administration of drug (0hr) serve as control for individual group and then at 1st hr, 2nd hr, 4th hr&6th hr and 10th day. On 10th day blood sample were collected after 4th hr of drug administration. In case of insulin half hour blood sample were also collected. After taking blood sample at 6th hr, animal was fed with standard rabbit feed 120gm per day. On 10th day rabbits were again fasted 10 hrs prior to drug administration and samples were taken. Water intake were maintained during the whole period of study. For oral drugs, suspension was made in distilled water with the help of soluble starch.

Method of blood sample collection

Blood samples were taken from marginal vein of pinna. Estimation of blood glucose level was done by GOD/POD method. [4]

STATISTICAL ANALYSIS

Mean & standard error of all group of observation were calculated. Significance of the differences in the blood glucose level were calculated by applying

student's 't' test in terms of p value. P value < 0.05 and p < 0.001 were considered as significant.

RESULT

Table-1: Blood glucose level in Albino Rabbits treated with normal saline
Blood Glucose Level (mg %)

Albino Rabbits of Group-I	Time interval					
	0 hr	1 hr	2 hr	4 hr	6hr	10 th day
R Ist	98.4	98.1	97.8	97.2	98.6	98.3
R IIInd	96.2	96.2	95.8	95.9	96.4	96.2
R IIIrd	98.8	98.5	98.7	98.4	98.8	97.6
R IVth	88.2	88.4	88.2	87.9	88.4	88.5
R Vth	85.6	86.2	86	85.8	90.2	86.8
R VIth	96.8	98.2	98	97	98.2	97.8
MEAN	94	94.27	94.08	93.70	95.10	94.20
SD	5.64	5.50	5.54	5.41	4.61	5.15
±SE		0.22	0.19	0.17	0.80	0.25
P VALUE		>0.05	>0.05	>0.05	>0.05	>0.05

Table-2: Blood glucose level in Albino Rabbit after single dose of insulin (1IU/kg s.c) administration
Blood Glucose Level (mg %)

Albino Rabbits of Group-II	Time interval					
	0 hr	1/2 hr	1 hr	2 hr	4hr	6hr
R Ist	90.2	68.2	52.0	54.0	84.0	88.2
R IIInd	92.0	72.4	52.4	48.0	86.0	90.0
R IIIrd	96.0	74.4	54.0	50.0	88.8	92.0
R IVth	98	80.8	56.0	48.8	90.4	94.2
R Vth	102	84.0	54.8	46.0	92.0	94.8
R VIth	94	74.4	54.2	50.0	88.0	92.8
MEAN	95.36	75.7	53.9	49.46	88.2	92
SD	4.3	5.8	1.5	2.7	2.9	2.5
±SE		0.85	2.03	3.62	1.35	1.55
P value		<0.001	<0.001	<0.001	<0.001	<0.001

Insulin was given just after taking blank control fasting blood sample

Table-3: Blood Glucose level in Albino Rabbits after Glibenclamide (0.05mg/kg/day P.O)administration
Blood Glucose level (mg %)

Albino Rabbits of Group-III	Time Interval					
	0 hr	1 hr	2hr	4hr	6hr	10 th day
R Ist	96.2	78.4	78.2	76.0	62.8	72.8
R IIInd	92.2	76.4	76.2	74.4	56.4	70.2
R IIIrd	86.2	74.2	74	72.2	54.8	68.2
R IVth	88.4	76.8	74.8	72	60.2	68.8
R Vth	94.2	80.2	78	72	64.4	70
R VIth	92	76.2	76	74.2	56.2	70
MEAN	91.53	77.03	76.20	73.47	59.13	70.00

SD	3.7	2.1	1.7	1.7	3.9	1.6
±SE		1.08	0.93	1.28	1.41	1.04
P value		<0.001	<0.001	<0.001	<0.001	<0.001

Table -4: Blood Glucose level in Albino Rabbits after Fluconazole (5mg/kg/day P.O) administration

Albino Rabbits of Group-IV	Blood Glucose level (mg%)					
	Time Interval					
	0 hr	1 hr	2hr	4hr	6hr	10 th day
R Ist	92.0	92.4	92.2	92.6	92.8	90.0
R IInd	94.2	94.6	96.0	94.8	94.4	94.0
R IIIrd	92.0	94.0	86.0	82.0	84.0	92.0
R IVth	90.0	90.2	90.0	88.8	88.0	90.0
R Vth	99.6	97.6	97.8	98.7	98.8	100.0
R VIth	91.0	91.6	91.5	91.8	92.8	90.8
MEAN	93.13	93.40	92.25	91.45	91.80	92.80
SD	3.5	2.6	4.2	5.7	5.2	3.8
±SE		0.37	1.0	1.68	1.29	0.34
P value		>0.05	>0.05	>0.05	>0.05	>0.05

Fluconazole was given just after taking blank control fasting blood sample

Table-5: Blood Glucose levels in Albino Rabbits after Itraconazole (5mg/kg/day P.O) administration

Albino Rabbits of Group-V	Blood Glucose level (mg%)					
	Time Interval					
	0 hr	1 hr	2hr	4hr	6hr	10 th day
R Ist	99.2	99	99.2	99.1	98.8	98.8
R IInd	98	98	98.1	98.3	97.6	97.7
R IIIrd	96.4	96.2	96.1	96.4	96.3	96.2
R IVth	90	91	91	89.8	89.7	88.5
R Vth	86.8	86.8	86.7	86.6	85	87
R VIth	87.8	89.2	89.5	89	88.8	87.4
MEAN	93.03	93.37	93.43	93.20	92.70	92.6
SD	5.5	5.0	5.1	5.4	5.6	5.5
±SE		0.26	0.30	0.19	0.28	0.22
P value		>0.05	>0.05	>0.05	>0.05	>0.05

Itraconazole was given just after taking blank control fasting blood sample

Table-6: Blood glucose levels in Albino Rabbits after Ketoconazole (5mg/kg/day P.O) administration

Albino Rabbits of Group-VI	Blood glucose level (mg%)					
	Time interval					
	0 hr	1 hr	2 hr	4 hr	6hr	10 th day
R Ist	97.4	97.1	86.4	82.8	96.2	84.0
R IInd	90.0	90.0	78.8	78.0	89.8	80.2
R IIIrd	96.2	96.0	82.0	80.4	95.8	80.4
R IVth	90.8	90.2	80.4	80.0	90.5	81.2
R Vth	92.8	94.0	82.8	82.0	92.2	82.8
R VIth	97.6	95.6	86.4	82.8	97.6	84.6
MEAN	94.13	93.83	82.80	81.00	93.7	82.20
SD	3.4	3.1	3.11	1.89	3.3	1.88

±SE	0.34	0.66	0.98	0.19	1.13
P value	>0.05	<0.001	<0.001	>0.05	<0.001

Ketoconazole was given just after taking blank control fasting blood sample

DISCUSSION

In this study we have been planned with an objective to study the effect of azoles(antifungal drugs)on blood glucose level in albino rabbits because patient suffering from fungal diseases has to take antifungal drug for longer duration and diabetic patient are immunocompromised and susceptible to number of opportunistic infection like fungal and bacterial infection. [2, 3, 4]. Table-4 shows that blood glucose level following fluconazole administration has insignificant ($p>0.05$) hypoglycemic activity. Table-5 shows that Itraconazole treatment has not showing any significant effect ($p>0.05$) on blood glucose level in albino rabbits. Fluconazole and Itraconazole have no effect on adrenocorticotrophic hormone stimulation. [5] Therefore Fluconazole and Itraconazole did not block cortisol synthesis in adrenal cortex, so that both the drugs have no significant effect on blood glucose level in albino rabbits. Table-6 shows that, ketoconazole have insignificant ($p>0.05$) hypoglycemic effect at one hour, significant at 2 hour ($p<0.001$) and 4 hour ($p<0.001$).At 6th hour blood glucose level become almost same as blood glucose level of 1hr ($p>0.05$) and on 10th day hypoglycemic effect is almost similar to the hypoglycemic effect observed by the 1st dose of ketoconazole at 4 hr of 1st day.

Ketoconazole induced hypoglycemia is approximately similar to Glibenclamide induced hypoglycemia at 2 hr and 4th hr. Ketoconazole block cortisol synthesis in adrenal cortex, [6] cortisol

initiate gluconeogenesis in liver [7] by inducing hepatic gluconeogenic enzyme and in muscles cortisol inhibit protein breakdown to provide amino acid mainly alanine for gluconeogenesis. [8] Cortisol increases synthesis of “macrocortin” polypeptide. [9] This polypeptide inhibit phospholipase A2 and decreasing membrane release of arachidonic acid the precursor of prostaglandin. [10] In ketoconazole treated animals, prostaglandin synthesis is increased due to decreased cortisol synthesis and this increase prostaglandin synthesis increase insulin release which may lead to hypoglycemia. [11] Cortisol also amplify the effect of glucagon and augment glucogenolysis so in ketoconazole treated animal, glucagon level is decreased because of decreased cortisol synthesis. [12] By virtue of cortisol blocking effect of ketoconazole, there is ketoconazole induced hypoglycemia. This mechanism of action of ketoconazole would again be in favor of diabetic individual suffering from fungal infection because cortisol suppresses body immunity. However it cannot be denied that ketoconazole per se may have hypoglycemic activity.

CONCLUSION

On the basis of this study it is concluded that Fluconazole & Itraconazole have no significant effect on blood glucose level but ketoconazole has significant short term hypoglycemic effect and we should be vigilant in diabetic patient on hypoglycemic drugs especially in early hours.

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