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STUDY OF ACTION OF LAMOTRIGINE ON ANTI-DIABETIC DRUGS IN ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT

Background: *Drug to drug interactions are common in epileptic patients with diabetes , but there are no reports about interactions of Lamotrigine with Tolbutamide and* Glibenclamide. ***Aim:*** *Present study was conducted in healthy rabbits,albino rats which were alloxan induced diabetic to evaluate the influence of administration of Lamotrigine on the pharmacokinetics parameters of Tolbutamide and Glibenclamide.* ***Method:*** *Four groups(n=6) of animals (I, II, III, IV) were selected. Groups I and II were administered with Tolbutamide (40 mg/kg) and groups III and I V were administered with Glibenclamide (40µg/kg). Groups were treated with Lamotrigine respectively for 7 days. On the 8th day one hour after Lamotrigine treatment, groups I ,II and III , IV were administered with Tolbutamide (40mg/kg) and Glibenclamide (40µg/kg) respectively. Blood samples were drawn from tail vein of rat certain hours at the both the occasions i.e, before and after and were analyzed for blood glucose levels by GOD/POD method. The same experiment was repeated in rabbits and diabetic rats.* ***Results:*** *In rabbits Lamotrigine showed a very little reduction in the hypoglycaemic activity of Tolbutamide and also reduction in activity of Glibenclamide. Lamotrigine showed a little reduction in hypoglycaemic activity of Glibenclamide in diabetes induced rats.* ***Conclusion:*** *The study suggests that the dose and frequency of sulfonylureas must be readjusted so that their activity is not altered when administered concomitantly with Lamotrigine.*

KEY WORDS

Sulfonylureas , Lamotrigine ,Tolbutamide ,Glibenclamide.

INTRODUCTION

The epilepsy is common devastating disorder, affecting approximately 2.5 million people in United States alone. More than 40 distinct forms of epilepsy have been identified. Epileptical seizures often cause transient impairment of consciousness leaving the individual at risk of bodily harm and often interfering with education and employment. Therapy is symptomatic in that available drugs inhibit seizures, but neither effective prophylaxis nor complete cure is available. Compliance with medication is a major problem because of the need for long-term therapy together with unwanted effects of many of these drugs.

The mechanism of action of anti seizure drugs fall into 3 major categories. Drugs effective against the most common forms of epileptic seizures, partial and generalized tonic-clomic seizures, appears to work by one of two mechanism. One is to limit the sustained,

repetitive firing of a neuron, an effect mediated by promoting the inactivated state of voltage-activated Na+ channels. A second mechanism appears to involve enhanced amino butyric acid (GABA)-mediated synaptic inhibition, an effect mediated by an action pre synaptically for some drugs and post synaptically for others. Drugs effective against a less common form of epileptic seizure, absence seizure, limit activation of a particular voltage activated Ca++ channel known as T-current.(1,2)

There are several incidences that a patient may suffer with more than one disease at a time. It is a need to treat all these aliments simultaneously. Hence it may required to administer more than one drug at the same time So, the incidence of drug-drug interactions may be very high in case of hospitalized patients.(1,3,4) This is a harmful type of pharmacodynamic drug interaction. (5, 6)

In case of pharmacokinetic type of drug-drug interaction, one drug may be interfering with absorption, distribution, metabolism and excretion of another drug and thereby increasing or decreasing the potency, onset and duration of action. It appears that the prolonged usage of Lamotrigine may induce the enzyme responsible for its own metabolism, keeping this aspect in view, it is thought that the metabolism of other drugs that are metabolized by cytochrome P450 enzyme system may be affected. Sulfonylureas are belonging to a class of orally acting anti diabetic agents (Tolbutamide, Glibenclamide etc.) that are metabolized by cytochrome P450 enzyme system3. Any alteration in the pharmacokinetics of these orally acting anti-diabetic agents may result in either severe hypoglycemia or hyperglycemia. Hence, it is critical to monitor the plasma levels of these agents to maintain the optimum blood glucose level.(4,5,6)

Since, there are certain percentage of patients who suffer from both partial seizure and diabetes, the treatment to both the diseases require a prolonged period and Lamotrigine and sulfonylureas may be combined. During such treatment regime, Lamotrigine is likely to affect the pharmacokinetics of sulfonylureas, thereby influence their anti diabetic effect.

Hence we have planned to investigate the possible interaction between Lamotrigine and sulfonylureas (Tolbutamide and Glibenclamide) in healthy rats, rabbits and diabetic rats. The criteria for investigation is to estimate the ex tent of influence of pretreatment of Lamotrigine on the hypoglycemic/anti-diabetic effect of sulfonylureas (Tolbutamide and Glibenclamide).

In the following pages, the relevant literature regarding epilepsy, anti epileptic drugs, Lamotrigine, its pharmacodynamic and pharmacokinetic properties, and interaction with the other drugs along with reports regarding the sulfonylureas and their interaction with other drugs are recorded.

MATERIALS AND METHODS

1. Tolbutamide: A suspension was prep ared by using 5% gum acacia as a suspending agent to represent 40mg/ml.
2. Glibenclamide: A solution was prepared to represent 40µg/kg with 95% alcohol.
3. Lamotrigine: A suspension was prepared in 5% gum acacia to representing 100mg/ml and 200mg/ml
4. Anticoagulant powder: Potassium oxalate and sodium fluoride in the ratio 3:1.
5. Alloxan: A solution of alloxan was prepared in normal saline to represent 150mg/ml Route - Intraperitonially.
6. Albino rats and Albino rabbits were taken in the study.
7. Glucose estimation kit
8. Spirit, aluminium foil, low voltage lamp, variable micropipette, 3ml and 10ml test tubes, mouth operated pipettes 1ml and 2ml, tissue paper, distilled water etc.
9. Elico mini sl. 171 spectrophotometer.

EXPERIMENTAL PROCEDURE :((7)

Albino rats of either sex weighing between 150-260 grams were divided into 4 groups (Group I, II, III, IV) of 6 animals and were marked . Albino rabbits of either sex weighing between 1.5-2.0 Kg

were divided groups (Group I, II, III & IV) of 3 animals each. They were suitably marked and placed in different rabbit cages. The animals were fasted for 18 hours before commencing the experiment. During this period, the animals were allowed to take adequate water. The fasting was continued till the completion of the experiment. Then Lamotrigine 200mg/kg was administered orally to all the rats. The blood samples are collected at 0, 0.5, 1.0, 2.0, 4.0,6.0, 8.0, 12.0 and 24.0 hours after the administration of Lamotrigine and analyzed for glucose levels by using GOD/POD method. Rabbits marked as group I and II received suspension of Tolbutamide 40mg/kg and the animals in the groups III and IV received Glibenclamide 40µg/kg through oral route. Blood samples were collected at 0.5, 1.0, 2.0, 4.0, 6.0. 8.0, 12.0, 18.0, 24.0, 30.0. 36.0. 42.0 and 48.0 hours from all the four groups. Blood glucose levels were estimated.

The percentage reduction in blood glucose levels at time "t" was calculated by using the following equation.

% Blood glucose reduction at time't' = $\frac{A-B}{A} \times 100$

Where,

A= Initial blood glucose level before dru g administration.

B= Blood glucose levels at time "t" after the drug administration.

In the first part of this present study, the hypoglycemic effect of Tolbutamide and Glibenclamide was established in animals.

In the next stage of this experiment, the effect of different doses of Lamotrigine (100mg/kg and 200mg/kg per day) for one week on the hypoglycemic activity of Tolbutamide and Glibenclamide was carried out in the same animals.

Induction of diabetes :(8, 9)

Rats of either sex weighing between 150-260 grams were selected and fasted for 18 hours . The rats were administered with 150mg/kg of alloxan intraperitonially. After 24 hours, the blood samples were collected and analysed for blood glucose level. It was found that diabetes was induced in about 24 hours. The blood samples were collected and analysed for four more days to stabilize. These animals were further used for our antidiabetic study.

Experimental procedure :(10, 11)

Diabetic rats of either sex were divided into two groups (group I and II) of 6 animals and they were marked conveniently. Blood samples were collected by fasting for blood glucose estimation.

In the first part of this antidiabetic study, the animals in group I and II received suspension of Tolbutamide 40mg/kg and Glibenclamide solution 40µg/kg respectively through oral route and blood glucose levels estimated

Animals in the groups I and II received suspensions of Lamotrigine100mg/kg and 200mg/kg per day orally respectively for one week. Groups III and IV also received Lamotrigine100mg/kg and 200mg/kg orally respectively for one week. On the 7th day, 6 hours after administration of Lamotrigine, the rats were fasted for 18 hours. On the 8th day blood samples were collected for determining fasting blood glucose levels and Lamotrigine 100mg/kg and 200mg/kg was administered orally to groups I and II respectively. Groups III and IV were also treated with Lamotrigine in the similar doses. After 60 minutes, Tolbutamide 40mg/kg was administered to first two groups (group I and II) and Glibenclamide 40µg/kg was administered to III and IV respectively. Blood samples were collected thereafter at different time intervals up to 48 hours. Blood glucose levels were estimated by GOD/POD method and expressed as mg/l00ml of blood. Then the hypoglycemic activity of Tolbutamide and Glibenclamide at time "t" was calculated and the percentage blood glucose reduction at various time intervals were calculated before and after Lamotrigine treatment with the equation.

RESULTS

Effect of Lamotrigine on blood glucose levels in normal healthy rats revealed that Lamotrigine has not altered blood glucose levels significantly . The blood glucose reduction observed with Lamotrigine was a minimum 0.63% to a maximum of 6.81% during 24 hours of the study.

Blood glucose reduction studies with Tolbutamide in a single dose revealed i.e, the drug has produced significant blood glucose reduction to a minimum of 6.24%, a maximum of 50.86% during 48 h rs of the study. Lamotrigine was administered at low dose (100mg/kg) in normal healthy rats followed by a single dose of Tolbutamide on 8th day. No significant blood glucose reduction was observed except at 0.5, 4.0, 6.0 and 24.0 hrs of in 48 hrs of study.

Results are tabulated in TABLE: 1, TABLE -2 and graphically depicted in FIG NO: 1

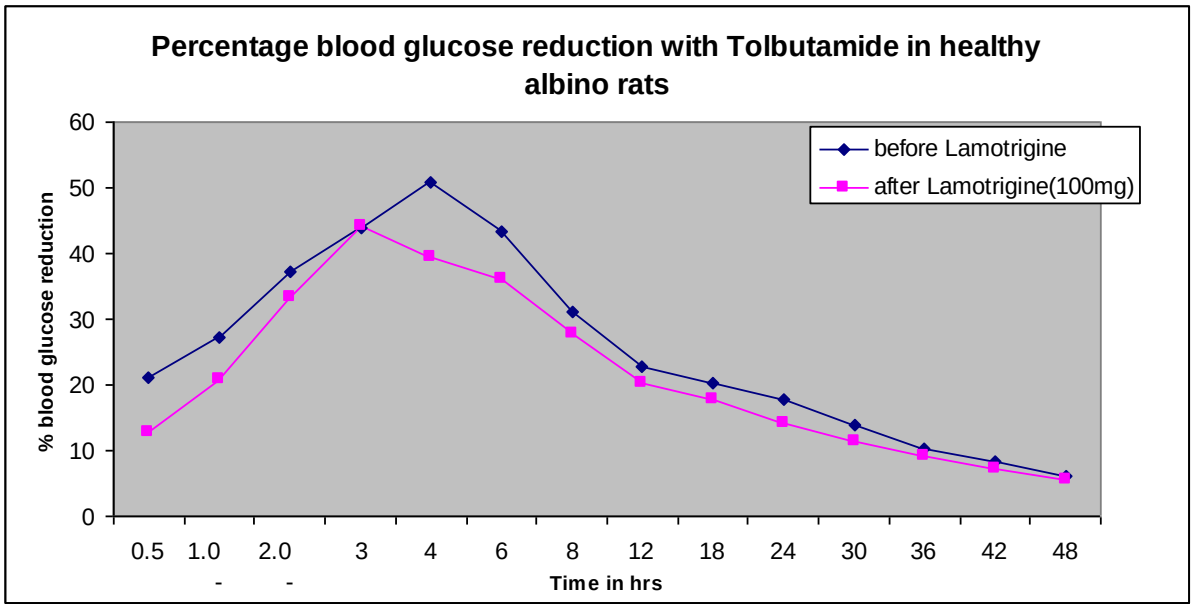
Table-1:Blood Glucose levels with tolbutamide in healthy albino Rats before and after administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Blood Glucose Levels (mg %) Mean+SEM with Tolbutamide	Blood Glucose Levels (mg %) Mean+SEM with Tolbutamide& Lamotrigine (100mg/kg)
Fasting	92.67 ± 2.38	92.09 ± 2.03
0.5	73.13 ± 2.03	80.31 ± 1.79
1.0	65.52 ± 1.80	72.99 ± 1.56
2.0	58.19± 1.71	61.49 ± 1.84
3.0	52.01 ± 1.58	51.29 ± 1.24
4.0	45.54 ± 1.39	55.89± 1.49
6.0	54.16 ± 1.78	58.91± 1.24
8.0	63.79 ± 1.99	66.23± 1.60
12.0	71.98 ± 2.08	73.42 ± 1.62
18.0	74.13 ± 2.21	76.43 ± 1.80
24.0	76.15 ± 2.28	79.14 ± 1.94
30.0	79.66± 2.36	81.58 ± 2.03
36.0	83.19 ± 2.34	83.76 ± 2.09
42.0	85.06 ± 2.23	85.34 ± 2.02
48.0	86.78 ± 2.06	87.07± 2.26

Table-2: Percentage Blood Glucose Reduction with tolbutamide in healthy albino Rats before and after administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction Mean+SEM with Tolbutamide	Percentage Blood Glucose reduction Mean+SEM with Tolbutamide and Lamotrigine (100mg/kg)
Fasting	-	-
0.5	21.10 ±0.19	12.76±0.90
1.0	27.36±2.53	20.74±0.38
2.0	37.20±0.91	33.26±1.19
3.0	43.88±0.72	44.25±0.40
4.0	50.86±0.65	39.33±0.77
6.0	43.23±1.19	36.02±0.62
8.0	31.19±0.82	27.91±0.91
12.0	22.81±0.66	20.27±0.62
18.0	20.15±0.66	17.82±1.33
24.0	17.87±0.58	14.09±0.76
30.0	13.99±0.51	11.4±0.59
36.0	10.25±0.50	9.07±0.73
42.0	8.23±0.53	7.34±0.62
48.0	6.24±0.32	5.49±0.71

Figure-1



Similar stud y was conducted in normal healthy rats treated with a single dose of Tolbutamide and with Lamotrigine higher dose i.e, 200mg/kg for one week followed b y a single dose of Tolbutamide on 8th day. percentage blood glucose reduction in both groups were compared. From the results it was found that bloodglucose reduction with Lamotrigine and tolbutamide combination was not significantly lesser than the unidose tolbutamide treated animals. Results are

tabulated in **Table -3, Table-4** and graphically depicted in **Fig: 2**.

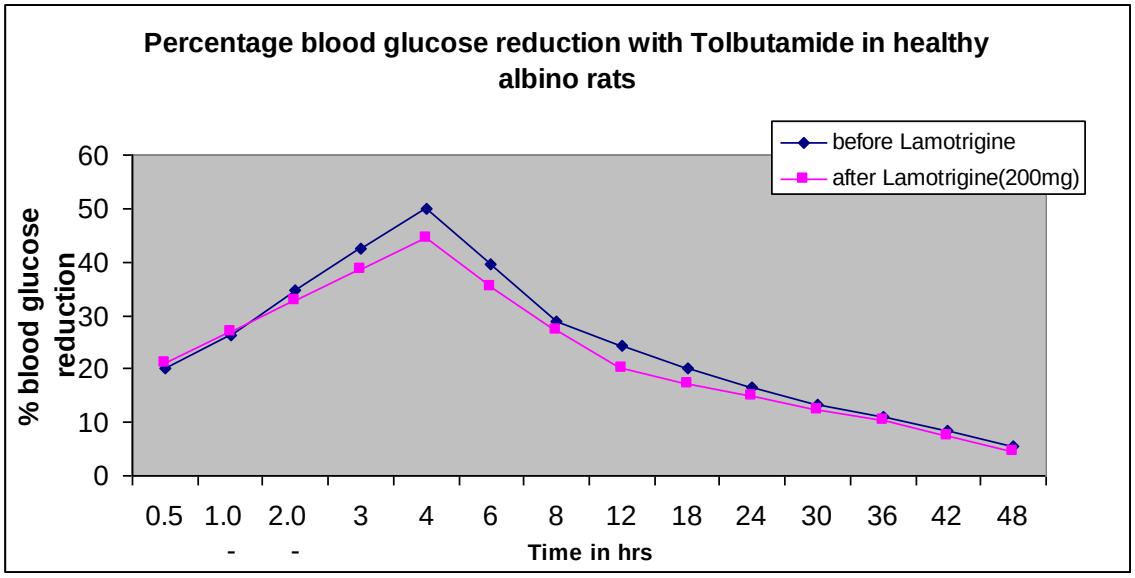
Table-3: Blood Glucose Reduction with Tolbutamide in healthy albino Rats before and after administration of Lamotrigine (200mg/kg) treatment

Time(hrs)	Blood Glucose Levels (mg %) Mean+SEM with Tolbutamide	Blood Glucose Levels (mg %) Mean+SEM with Tolbutamide and Lamotrigine (200mg/kg)
Fasting	91.95 ±2.13	93.10±2.09
0.5	73.56 ±1.92	73.56±1.71
1.0	66.80± 1.73	67.95±1.55
2.0	60.06±1.57	63.07 ±1.13
3.0	52.87±1.54	57.04±1.1
4.0	45.97±1.11	51.72 ±1.12
6.0	55.60±1.46	61.72±2.07
8.0	65.51±1.66	67.81±1.46
12.0	69.39±1.51	74.28±1.72
18.0	73.56±1.62	76.58±1.88
24.0	76.85±1.66	79.16±2.02
30.0	79.74±1.93	79.94±2.37
36.0	81.89±1.79	83.62±2.18
42.0	84.19±1.93	86.20±2.03
48.0	87.07±1.91	88.50±2.06

Table-4:Percentage Blood Glucose Reduction with Tolbutamide in healthy albino Rats before and after administration of Lamotrigine (200mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction Mean+SEM with Tolbutamide	Percentage Blood Glucose reduction Mean+SEM with Tolbutamide and Lamotrigine (200mg/kg)
Fasting	-	-
0.5	20.02±0.44	20.99±0.42
1.0	26.23±1.15	26.95±0.65
2.0	34.69±0.63	32.88±1.13
3.0	42.53±0.59	38.70±1.09
4.0	50.00±0.34	44.44±0.45
6.0	39.54±0.60	35.49±0.56
8.0	28.74±0.90	27.16±0.46
12.0	24.35±0.57	20.22±0.20
18.0	19.98±0.29	17.10±0.77
24.0	16.39±0.19	15.00±0.26
30.0	13.17±0.16	12.40±0.59
36.0	10.95±0.16	10.22±0.48
42.0	8.43±0.26	7.44±0.35
48.0	5.59±0.26	4.54±0.44

Figure-2



Similarly, Glibenclamide was administered to a group of 6 normal healthy rats to study its hypoglycaemic effect. From the data, we found that this drug has produced a significant blood glucose reduction with a minimum of 5.01% and a max imum of 54.96% at different time intervals of 48 hrs of the experiment study.

A similar experiment was also conducted with Lamotrigine pre-treatement at low dose (100mg/kg) for one week followed by a single dose administration of Glibenclamide on 8th day. Hypoglycaemic effect with these two drug combination was compared with that of Glibenclamide single dose treated group. From the data , it was found that the combination has always produced a lesser hypo glycaemic effect than single dose treated group. The percentage blood glucose reduction with Glibenclamide and Lamotrigine combination at low dose was 2.23% to 7.43% during 48 hrs of the experimental study. Results are tabulated in **Table-5, Table-6** and graphically depicted in **Fig: 3**

Table-5:Blood Glucose levels with Glibenclamide in healthy albino Rats before and after administration o f Lamotrigine (100 mg/kg) treatment

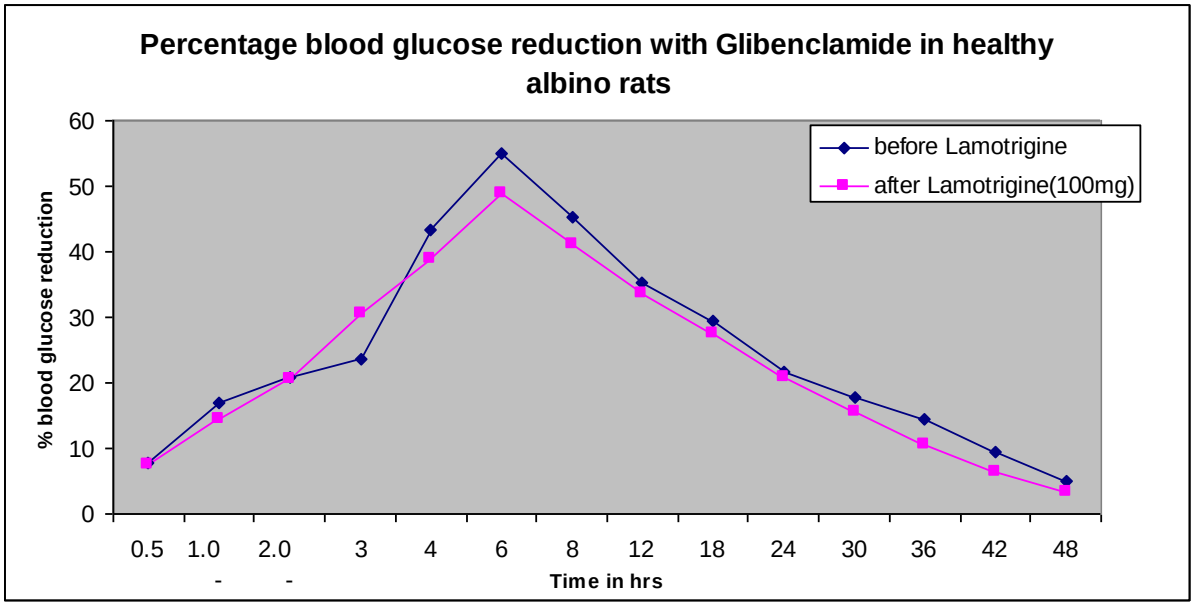
Time(hrs)	Blood Glucose Levels (mg %) Mean+SEM with Glibenclamide	Blood Glucose Levels (mg%) Mean+SEM with Glibenclamide and Lamotrigine (100mg/kg)
Fasting	89.51±2.36	89.22±2.29
0.5	40.22±1.78	45.68±1.18
1.0	48.99±1.90	52.58±1.61
2.0	50.57±1.98	54.45 ± 1.76
3.0	58.17±2.41	59.19±1.64
4.0	63.65±2.22	64.80 ±1.66
6.0	68.53±2.50	61.92± 1.33
8.0	70.26±2.44	70.68±1.91
12.0	70.83±2.38	70.68±1.87
18.0	73.56±2.64	75.43±2.03
24.0	74.37±2.28	76.43± 2.14
30.0	77.30±2.61	79.88±2 .12

36.0	81.03±2.46	83.33±2.33
42.0	81.20±13.72	82.61± 2.29
48.0	85.05±2.60	86.35±2.36

Table-6:Percentage Blood Glucose Reduction with Glibenclamide in healthy albino Rats before and after administration of Lamotrigine (1 00mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction Mean+SEM with Glibenclamide	Percentage Blood Glucose reduction Mean+SEM with Glibenclamide and Lamotrigine (100mg/kg)
Fasting	-	-
0.5	7.88±0.40	7.40±0.29
1.0	17.04±0.51	14.33±0.40
2.0	20.94±0.70	20.64±0.55
3.0	23.53±0.80	30.55±0.84
4.0	43.36±2.50	39.02±0.55
6.0	54.96±2.13	48.80±0.28
8.0	45.22±1.83	41.10±0.41
12.0	135.23±1.67	33.62±0.34
18.0	29.56±1.38	27.38±0.44
24.0	21.57±1.04	20.79±0.46
30.0	17.89±1.10	15.470.52
36.0	14.38±0.94	10.58±0.55
42.0	9.48±1.05	6.40±0.43
48.0	5.01±0.85	3.20±0.35

Figure: 3



A similar experiment was also conducted with combination of Lamotrigine high dose (200mg/k g) with Glibenclamide usual dose mentioned in the previous experiment. Once again the hypoglycemic effect in Lamotrigine and Glibeclamide treated groups were compared from the results it was found that the combination has enhanced hypoglycemic effect of glibenclamide for a period of 4hrs. Percentage blood glucose reduction was a minimum of 3.59% to a maximum of 52.07%.Percentage of blood glucose reduction was a minimum of 4.21% to 58.72%in single dose treated albino rats. Results are tabulated in **Table-7, Table-8** and graphically depicted in **Fig: 4**

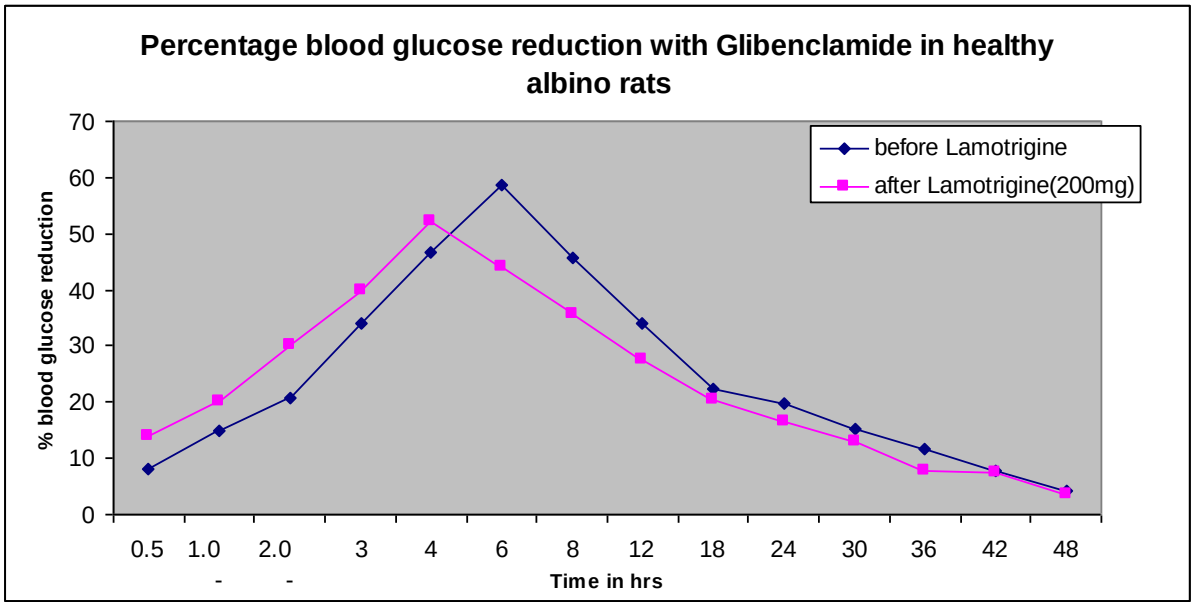
Table-7: Blood Glucose levels with Glibenclamide in healthy albino Rats before and after administration of Lamotrigine (200mg/kg) treatment

Time(hrs)	**Blood Glucose Levels (mg%) Mean+SEM with Glibenclamide**	**Blood Glucose Levels (mg%) Mean+SEM with Glibenclamide and Lamotrigine (200mg/kg)**
Fasting	88.50 ±2.13	87.78 ± 1.86
0.5	82.80 ±2.29	75.57 ±1.86
1.0	75.28 ±1.96	70.25 ±1.77
2.0	70.11 ±1.85	61.44 ± 2.08
3.0	58.19 ±0.83	52.29 ± 2.03
4.0	47.41 ± 1.05	42.09 ± 1.01
6.0	36.49 ±0.69	49.13 ±0.92
8.0	48.42± 0.93	56.53 ± 1.11
12.0	58.16 ±1.49	63.50 ± 1.65
18.0	68.67± 1.71	69.92 ±1.55
24.0	71.12 ±2.01	73.13 ± 1.40
30.0	75.0 ± 2.16	76.43 ±1.49
36.0	78.16 ±2.12	80.88 ± 1.81
42.0	81.61± 1.97	81.32 ± 1.92
48.0	84.77 ±1.97	86.07 ± 14.45

Table-8: Percentage Blood Glucose Reduction with Glibenclamide in healthy albino Rats before and after administration of Lamotrigine (200mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction mean+SEM with Glibenclamide	Percentage Blood Glucose reduction mean+SEM with Glibenclamide and Lamotrigine (200mg/kg)
Fasting	-	-
0.5	7.95±0.54	13.91±0.50
1.0	14.9±0.43	20.00±0.42
2.0	20.79±0.44	30.09±1.13
3.0	34.16±0.83	39.90±2.09
4.0	46.71±0.93	52.07±0.25
6.0	58.72±0.72	44.01±0.54
8.0	45.71±1.36	35.59±0.51
12.0	34.15±0.70	27.69±0.65
18.0	22.42±0.54	20.36±0.39
24.0	19.67±0.62	16.67±0.49
30.0	15.30±0.69	12.91±0.54
36.0	11.72±0.43	7.87±0.65
42.0	7.79±0.31	7.38±0.50
48.0	4.21±0.12	3.59±0.48

Figure: 4



In order, to verify any change in the effect of drugs in different animals, similar type of study as explained above was also conducted in normal healthy rabbits Lamotrigine 200mg/kg single dose treatment in rabbit has not altered the

blood glucose reduction when compared to initial blood glucose levels. Results are tabulated in **Table-9**.

Table-9. Blood Glucose levels after the administration of Lamotrigine (200mg/kg) in healthy albino rabbits.

Time(hrs)	**Blood Glucose Levels (mg%) mean+SEM with Lamotrigine (200mg/kg) .**	**P ercentage of Blood Glucose Reduction with Lamotrigine (200mg/kg)**
Fasting	120.69 ± 1.99	----
0.5	121.55 ± 1.99	-0.71
1.0	122.41 ±1.99	-1.42
2.0	123.27 ± 1.99	-2.14
3.0	124.13 ±1.99	-2.85
4.0	124.99 ±1.99	-3.56
6.0	125.85 ±1.99	-4.28
8.0	123.84 ±2.01	-2.60
12.0	124.13 ±2.17	-2.85
18.0	123.27±2.49	-2.12

Hypoglyceamic effect of tolbutamide in normal healthy rabbits with single dose treatment has produced a minimum of 3.14% to a maximum of 27.59% blood glucose reduction at different time intervals. Combination therapy (Lamotrigine 100mg/kg daily for one week followed by tolbutamide administration on 8th day) revealed lesser h ypoglycaemic effect than single dose treated animal group. In combination therapy the percentage blood glucose reduction minimum 1.72% and a max imum 21.91% at different time intervals.

Results are tabulated in **Table 10, Table: 11** and graphically depicted in **Fig: 5**

Table 10. Blood Glucose levels with tolbutamide in healthy albino rabbits before and after administration of Lamotrigine (100 mg/kg) treatment

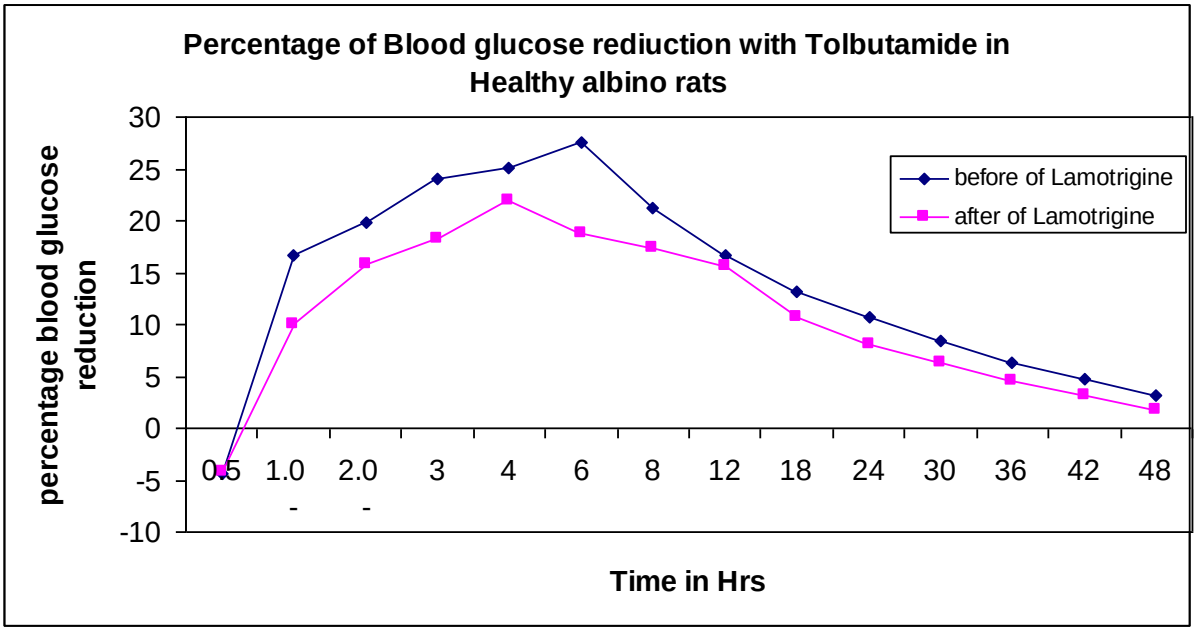
Time(hrs)	**Blood Glucose Levels (mg%) mean+SEM with Tolbutamide**	**Blood Glucose Levels (mg%) with mean+SEM Tolbutamide & Lamotrigine (100mg/kg)**
Fasting	140.80 ±18.84	140.22 ± 18.31
0.5	146.79 ± 18.91	146.27 ± 19.57
1.0	117.24 ± 15.12	126.73 ± 18.56
2.0	112.64 ± 14.07	117.82 ± 14.84
3.0	108.33 ± 12.75	114.66 ± 15.15
4.0	104.60 ± 10.75	109.65 ± 15.54
6.0	101.15 ± 10.46	114.08 ± 15.95
8.0	110.35 ± 12.54	116.10 ±16.23
12.0	116.09 ± 13.09	118.39 ±15.95
18.0	121.84 ± 14.10	125.29 ± 16.35
24.0	125.29 ± 14.55	129.03 ± 17.09
30.0	128.45 ± 15.55	131.32 ± 17.16
36.0	131.62 ± 16.12	133.91 ± 17.58
42.0	133.91 ± 16.70	135.92 ± 17.87

48.0	136.20 ± 17.27	137.65 ± 17.86

Table 11:Percentage Blood Glucose reduction with tolbutamide in healthy albino rabbits before and after administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Percentage of Blood Glucose Reduction mean+SEM with Tolbutamide	Percentage of Blood Glucose Reduction mean+SEM with tolbutamide and Lamotrigine (100mg/kg
Fasting	-	-
0.5	-4.36± 1.31	-4.24±0.73
1.0	16.6± 0.87	9.95±1.73
2.0	19.80± 1.75	15.87±0.43
3.0	24.11±0.54	18.26±0.22
4.0	25.12±2.58	21.91±0.96
6.0	27.59±2.93	18.81±1.03
8.0	21.23±1.65	17.39±1.03
12.0	16.73±1.43	15.64±0.82
18.0	13.08±1.44	10.64±0.52
24.0	10.63±1.51	8.07±0.67
30.0	8.48±1.09	6.34±0.06
36.0	6.26±0.99	4.54±0.16
42.0	4.68±0.82	3.08±0.19
48.0	3.14±0.60	1.72±0.16

Figure-5



Similarly, combination therapy Lamotrigine 200mg/kg daily for 1 week followed by tolbutamide administration on 8th day revealed lesser hypoglycemic. Results as tabulated in **Table: 11, Table: 12** and graphically depicted in **Fig: 6**.

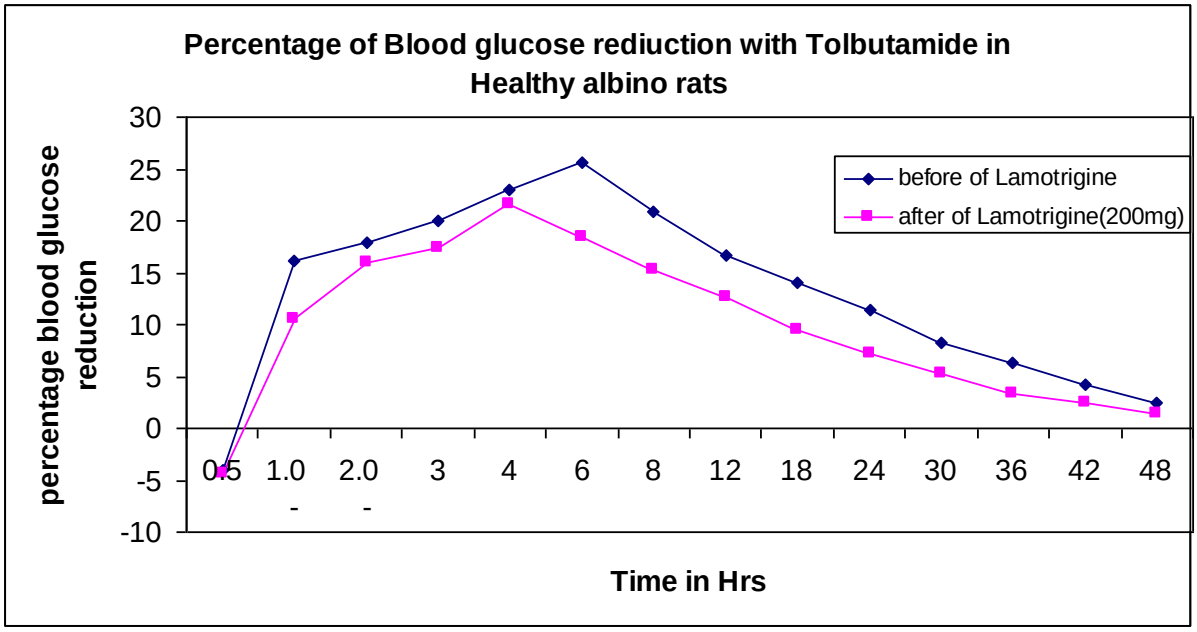
Table-11 : 200mg/kg Lamotrigine treatment

Time(hrs)	**Blood Glucose Levels (mg%) mean+SEM with tolbutamide**	**Blood Glucose Levels (mg%) mean+SEM with tolbutamide and Lamotrigine (200mg/kg)**
Fasting	143.39 ± 18.42	141.37 ± 18.13
0.5	143.91 ± 21.80	147.07 ± 17.06
1.0	120.12 ± 14.97	126.73 ± 17.33
2.0	117.53 ± 14.55	118.97 ± 15.57
3.0	114.66 ± 14.68	117.53 ± 18.47
4.0	110.35± 14.26	110.92 ± 14.87
6.0	106.61 ± 14.01	115.23 ± 14.87
8.0	113.22 ±13.69	119.54 ± 14.83
12.0	119.26 ± 14.5	123.32 ± 15.15
18.0	122.99 ± 14.39	127.59 ± 15.10
24.0	126.73 ± 14.67	130.75 ± 15.25
30.0	131.04 ± 15.11	133.63 ± 16.40
36.0	133.9 ±15.39	136.50 ± 17.12
42.0	137.07 ±16.40	137.93 ± 17.70
48.0	139.66 ± 17.26	139.37 ± 17.84

Table-12:Percentage of Blood Glucose Reduction Lamotrigine (200mg/kg) treatment

Time(hrs)	Percentage of Blood Glucose Reduction mean+SEM with tolbutamide	Percentage of Blood Glucose Reduction mean+SEM with tolbutamide and Lamotrigine (200mg/kg)
Fasting	-	-
0.5	-4.07±0.38	-4.33±1.41
1.0	16.14±0.80	10.53±1.08
2.0	17.98±0.94	15.89±0.50
3.0	20.01±0.72	17.43±2.33
4.0	23.05±0.30	21.64±0.80
6.0	25.69±0.72	18.50v0.68
8.0	20.89±0.62	15.35±0.42
12.0	16.69±0.52	12.65±0.70
18.0	13.99±0.90	9.54±0.83
24.0	11.35±1.08	7.25±1.05
30.0	8.33±1.11	5.35±0.61
36.0	6.30±1.16	3.38±0.31
42.0	4.20±0.86	2.43±0.19
48.0	2.48±0.58	1.41±0.02

Figure:6



Similarly the effect of Lamotrigine on hypoglycemic eff ect of glibenclamide at 2 dose levels was studied i.e., 100mg/kg and 200 mg/kg as Lamotrigine was treated for one week with these 2 different doses in 2 different groups of animals treated with only one dose of glibenclamide.

Lamotrigine 100mg/kg prior treatment to Tolbutamide has not affected or altered the hypoglycemic eff ect of glibenclamide in rabbits, except at 6th hour.

Results are tabulated in **Table: 13, Table: 14** and graphically depicted in **Fig: 7**

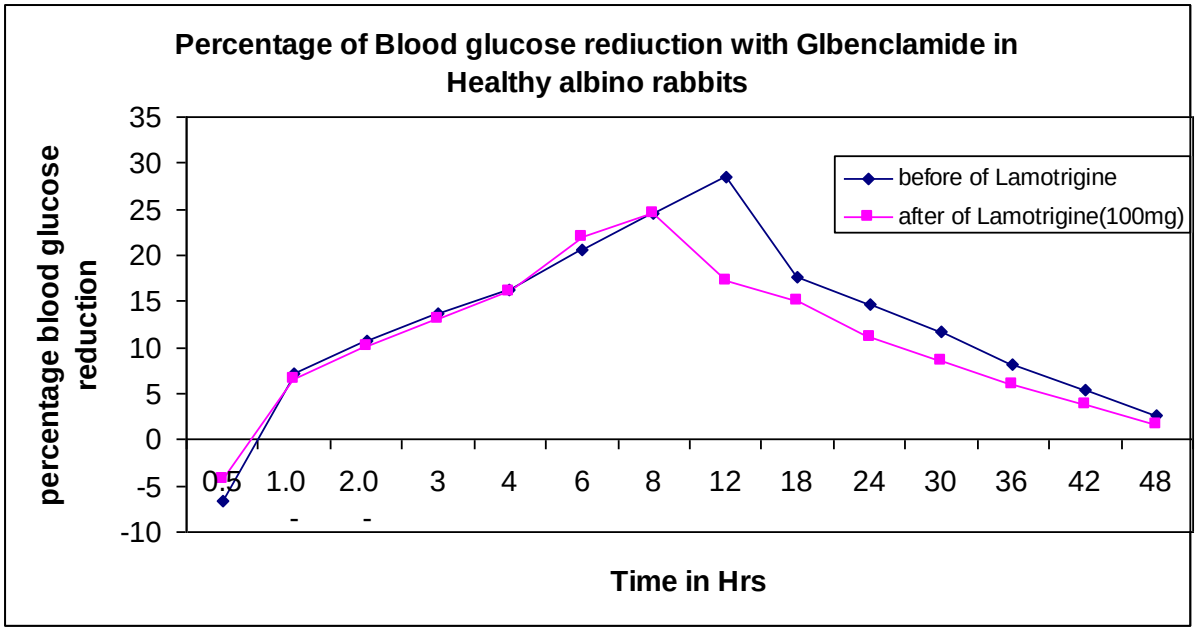
Table-13:Blood Glucose levels with Glibenclamide in healthy albino rabbits before and after administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Blood Glucose Levels (mg%) mean+SEM with glibenclamide	Blood Glucose Levels (mg%) mean+SEM with glibenclamide and Lamotrigine (100mg/kg
Fasting	120.11 ± 3.50	118.68 ± 2.01
0.5	125.24 ± 3.26	123.56 ± 2.74
1.0	111.50 ± 3.67	110.92± 2.51
2.0	107.19 ± 3.00	106.61± 1.52
3.0	103.74 ± 3.00	103.17 ± 1.52
4.0	100.58 ± 2.75	99.72 ± 1.89
6.0	95.41± 1.75	92.53 ± 2.08
8.0	90.32 ± 1.46	89.66 ± 1.72
12.0	85.92 ± 1.75	98.86 ± 1.04
18.0	98.85 ± 2.51	102.02 ± 1.25
24.0	100.01 ± 33.41	105.46 ± 1.15
30.0	106.04 ± 2.77	108.62 ± 1.49
36.0	110.35 ± 2.99	111.50 ± 1.75
42.0	113.51 ± 3.05	114.09 ± 2.01
48.0	116.96 ± 3.54	116.67 ± 1.75

Table-14:Percentage Blood Glucose Reduction with Glibenclamide in healthy albino rabbits before after the administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction mean+SEM with Glibenclamide	Percentage Blood Glucose reduction mean+SEM with Glibenclamide and Lamotrigine (100mg/kg)
Fasting	-	-
0.5	-6.70±1.71	-4.25±3.99
1.0	7.15±0.77	6.55±0.53
2.0	10.75±0.11	10.16±0.25
3.0	13.63±0.04	13.07±0.21
4.0	16.25±0.17	15.98±0.41
6.0	20.51±0.87	22.03±1.03
8.0	24.56±1.30	24.45±0.54
12.0	28.43±0.63	17.17±0.38
18.0	17.67±0.55	15.01±0.16
24.0	14.58±0.20	11.12±0.71
30.0	11.69±0.31	8.46±0.35
36.0	8.1±0.29	6.05±0.15
42.0	5.47±0.35	3.87±0.48
48.0	2.62±0.27	1.68±0.21

Figure: 7



Similarly Lamotrigine 200mg/kg prior treatment to glibenclamide has not at all altered blood glucose levels except at 6th hour. Results are tabulated in **Table: 15, Table: 16** and graphically depicted in **Fig: 8**.

Table-15: Blood Glucose Levels with Glibenclamide in healthy albino rabbits before and after administration of Lamotrigine (200mg/kg) treatment

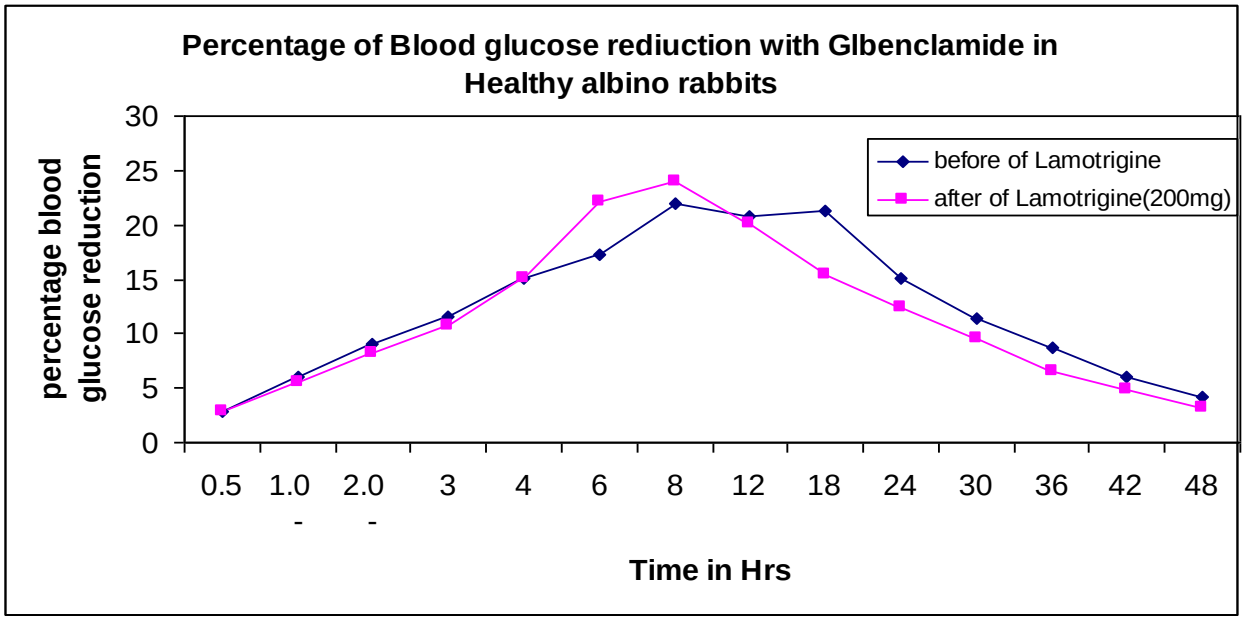
Time(hrs)	Blood Glucose Levels (mg%) mean+SEM with Glibenclamide	Blood Glucose Levels (mg%) mean+SEM with Glibenclamide and Lamotrigine (200mg/kg)
Fasting	118.11 ± 5.25	117.79 ±5.18
0.5	114.66± 5.48	114.37 ±5.19
1.0	110.92± 5.48	111.21 ±4.91
2.0	107.47± 5.23	108.05± 5.11
3.0	104.50± 5.10	105.18 ±5.39
4.0	100.29± 5.33	100.00 ±4.75
6.0	96.56 ±4.98	93.11 ±5.39
8.0	91.1± 5.28	89.66 ±5.39
12.0	85.25± 5.16	93.97 ±4.81
18.0	93.11± 5.25	99.43 ±4.47
24.0	101.15± 4.36	103.45 ±4.57
30.0	104.60 ±4.84	106.61 ±4.84
36.0	107.77 ±4.91	110.06 ±4.71
42.0	110.92 ±4.79	112.07 ±4.43
48.0	113.22±5.02	114.05 ±4.61

Table-16: Percentage Blood Glucose Reduction with Glibenclamide in healthy albino rabbits before and after

administration of Lamotrigine (200mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction mean+SEM with Glibenclamide	Percentage Blood Glucose reduction mean+SEM with Glibenclamide and Lamotrigine(200mg/kg)
Fasting	-	-
0.5	2.84±0.5	2.91±0.15
1.0	6.02±0.50	5.58±0.04
2.0	9.13±0.63	8.29±0.36
3.0	11.55±0.39	10.76±0.68
4.0	15.14±0.83	15.12±0.81
6.0	17.29±0.69	22.05±1.14
8.0	21.96±1.04	23.99±1.28
12.0	20.84±1.23	20.18±0.70
18.0	21.26±0.94	15.49±0.71
24.0	15.12±0.48	12.36±0.32
30.0	11.44±0.53	9.49±0.28
36.0	0 8.75±0.77	6.54±0.17
42.0	6.07±0.32	4.81±0.44
48.0	4.13±0.14	3.13± 0.37

Figure: 8



Further, the study was extended to verify the drug interaction if any in diabetic rats with combination of Lamotrigine 100mg/kg administered for 7 days followed by Tolbutamide and glibenclamide in 2 separate groups of animals respectively. From 3rd hour onwards there is no enhanced anti-diabetic activity but, the combination produced lesser activity than single Tolbutamide treatment. Results are tabulated in **Table: 17, Table: 18** and graphically depicted in **Fig: 9.**

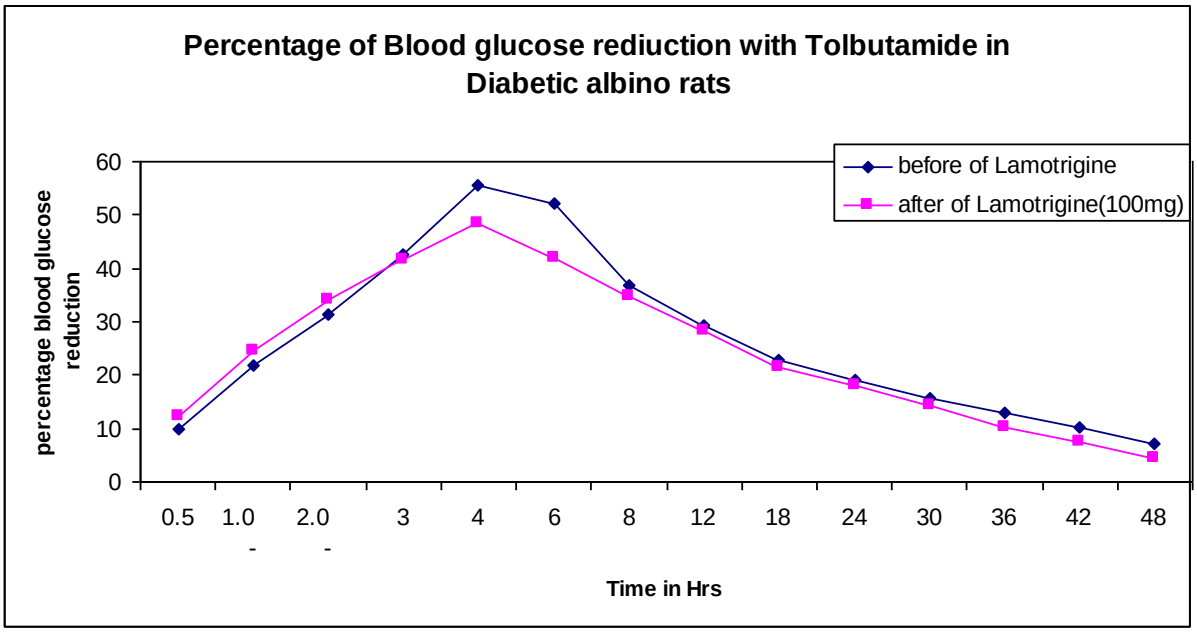
Table-17:Blood Glucose lev els with tolbutamide in diabetic albino Rats before and after administration of Lamotrigine (100 mg/kg) treatment

Time(hrs)	Blood Glucose Levels (mg%) mean+SEM with Tolbutamide	Blood Glucose Levels (mg%) mean+SEM with Tolbutamide and Lamotrigine (100mg/kg)
Fasting	342.96 ±23.48	338.99±24.57
0.5	309.49 ±21.61	295.26±20.11
1.0	268.10 ±19.52	254.16±19.76
2.0	235.89 ±16.38	229.88±17.06
3.0	195.98 ±12.41	207.61±13.86
4.0	151.28 ± 6.82	190.08±16.22
6.0	178.16 ± 10.83	207.90±14.26
8.0	217.09± 16.85	230.03±13.01
12.0	245.52±15.94	248.41±15.53
18.0	266.45±18.85	266.95±17.87
24.0	277.15±19.41	276.43±18.75
30.0	289.80±22.20	287.07±20.08
36.0	297.98± 22.03	299.71±22.89
42.0	307.32±22.15	309.38±25.65
48.0	317.48±22.03	317.96±27.67

Table-18:Percentage Blood Glucose Reduction with tolbutamide in diabetic albino Rats before and after administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction mean+SEM with Tolbutamide	Percentage Blood Glucose reduction mean+SEM with Tolbutamide and Lamotrigine (100mg/kg)
Fasting	-	-
0.5	9.79±0.65	12.44±2.83
1.0	21.92±0.90	24.52±3.91
2.0	31.21±0.77	34.22±2.60
3.0	42.65±1.26	41.76±1.59
4.0	55.50±1.26	48.42±0.35
6.0	52.18±4.98	41.98±0.89
8.0	36.79±1.22	34.74±1.45
12.0	29.34±0.96	28.43±0.93
18.0	22.74±0.86	21.39±0.68
24.0	19.20±0.68	18.13±0.62
30.0	15.59±1.63	14.32±1.00
36.0	13.12±1.67	10.35±0.78
42.0	10.38±1.40	7.63±0.81
48.0	7.29±1.18	4.35±0.99

Figure: 9



Similarly, Lamotrigine and glibenclamide combined effect on anti-diabetic activity was compared with single dose glibenclamide effect in diabetic rats revealed no enhanced anti-diabetic activity with glibenclamide and Lamotrigine but a decreased anti-diabetic effect was observed with combination throughout the 48 hrs study than single dose treatment of glibenclamide. Results are tabulated in **Table: 19, Table: 20** and graphically depicted in **Fig: 10**

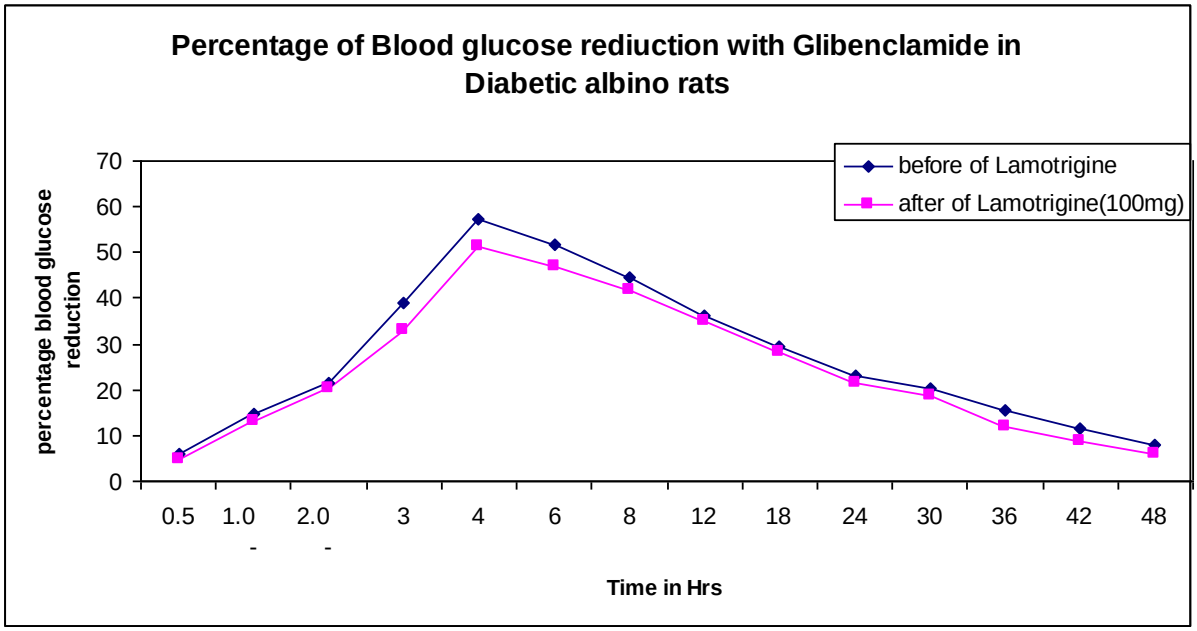
Table-19:Blood Glucose lev els Glibenclamide in diabetic albino Rats before and after administration of Lamotrigine (100 mg/kg) treatment

Time(hrs)	**Blood Glucose Levels (mg%) mean+SEM with Tolbutamide**	**Blood Glucose Levels (mg%) mean+SEM with Tolbutamide** and **Lamotrigine (100mg/kg)**
Fasting	329.31±21.50	329.30±21.13
0.5	309.62±20.13	316.67±19.30
1.0	288.36±19.29	292.09±19.11
2.0	257.69±15.96	265.19v16.39
3.0	200.83±12.43	228.59±14.63
4.0	140.51±8.19	170.2611.85
6.0	158.47±9.05	172.70±12.64
8.0	181.46±10.07	188.65±13.22
12.0	208.74±13.17	211.01±13.05
18.0	229.45±14.34	229.95±14.74
24.0	253.73±17.12	255.18±15.75
30.0	262.64±18.49	271.6±47.57
36.0	294.39v25.62	288.93±16.68
42.0	290.80±17.40	299.71±16.63
48.0	302.30±18.75	309.62 ±17.97

Table-20:Percentage Blood Glucose Reduction with Glibenclamide in diabetic albino Rats before and after administration of Lamotrigine (100mg/kg) treatment

Time(hrs)	Percentage Blood Glucose reduction mean+SEM with Tolbutamide	Percentage Blood Glucose reduction mean+SEM with Tolbutamide and Lamotrigine (100mg/kg)
Fasting	-	-
0.5	6.15±1.05	4.69±0.42
1.0	14.76±1.38	12.96±1.15
2.0	21.64±0.85	20.15±0.81
3.0	38.97±0.49	32.97±0.89
4.0	57.21±0.78	51.22±0.19
6.0	51.69±0.92	46.81±0.38
8.0	44.44±2.23	41.64±0.65
12.0	36.26±1.58	34.9±0.73
18.0	29.29±1.27	28.28 ±1.35
24.0	23.21±1.68	21.50±0.89
30.0	20.34±1.41	18.54±0.95
36.0	15.49±1.41	12.10±0.77
42.0	11.51±0.98	8.78±0.92
48.0	8.08±0.61	5.85±0.72

Figure: 10



Lamotrigine 200mg/kg body weight in normal healthy rats failed to significantly reduce no rmal blood glucose levels. Main aim of the study was to find out prior treatment of Lamotrigine used in the treatment of epilepsy has any effect on a oral anti-diabetic drug tolbutamide and glibenclamide used in type 1 diabetes.

Blood glucose levels analysed from animals treated with a single dose of tolbutamide and animals that received Lamotrigine 100mg/kg for one week followed by a single dose

administration of tolbutamide on the next day were compared. And the study revealed Lamotrigine has reduced the h ypo glycaemic effect of tolbutamide .the onset of action was increased from 0.5 to 1.0 hrs, duration of action was decreased from 18.0 to 12.0 hrs and peak effect was reduced from 50.86% to 44.25 % in animals pretreated with Lamotrigine +tolbutamide .

Similarly, prior treatment of high dose of Lamotrigine i.e., 200mg/kg for one week followed by a single dose of tolbutamide on the next day was compared with tolbutamide hypoglycemic effect. The results revealed that at high dose also Lamotrigine has not potentate tolbutamide effect and there is no much difference between tolbutamide treated and Lamotrigine + tolbutamide treated groups. The duration of action was reduced but no change in onset and peak effect was observed. The maximum percentage of blood glucose reduction was reduced from 50.00% to 44.44%

Similarly the effect of pretreated Lamotrigine at 100 mg/kg and 200mg/kg dose in 2 different groups of rats treated for 7 days followed by a single dose of glibenclamide on 8th day in both groups was compared with the hypoglycemic effect of single dose treatment of glibenclamide. From the data it was found that prior treatment of Lamotrigine 100mg/kg has not potentiated hypoglycemic effect of glibenclamide except at 3rd hour in the same was Lamotrigine pretreatment 200mg/kg has potentiated glibenclamide activity upto 4 hrs. In animals pre-treated with Lamotrigine (100mg/kg) there was a reduction in blood glucose levels from 54.96% to 48.80%.In animals pretreated with Lamotrigine(200mg/kg) there was reduction in blood glucose levels from 58.72% to 44.01%. The onset, duration of action and peak effect were not altered. In order to verify the difference in effect of drugs in different animals Lamotrigne 200mg/kg single dose was tested for its effect on blood glucose levels of normal health y rabbits. Lamotrigine has not significantly reduced blood glucose levels.

To know the acute treatment of Lamotrigine 100 mg/kg, 200mg/kg for 1 week in 2 different groups followed by a single dose of tolbutamide on 8th day was compared with hypoglycemic effect of tolbutamide single dose treated animals .From the blood glucose reduction data it was found that Lamotrigine pretreatment at low and high doses has not potentiated the hypoglycemic effect of tolbutamide in normal healthy rabbits. In animals pretreated with Lamotrigine (100mg/kg) onset, duration of action and peak effect were not significantly reduced. Maximum% of blood glucose reduction was reduced from 27.58 to 21.91%.In animals pretreated with Lamotrigine (200mg/kg) maximum percentage of blood glucose reduction was reduced from 25.69% to 21.64%.the onset, duration of action and peak effect were slightly altered.

Similar study was conducted in normal healthy rabbits and tolbutamide was replaced by glibenclamide. The results confirmed that hypoglycemic effect of glibenclamide was reduced by Lamotrigine (100mg/kg and 200mg/kg) throughout the experimental study. The results showed a decrease in peak effect and duration of action.the maximum reduction in blood glucose levels was found to be from 28.43% to 24.45% in animals pretreated with Lamotrigine (100mg/k g). In animals pretreated with Lamotrigine (200mg/kg) showed a similar alterations as in case of low dose treated animals ie., (100mg/kg) with a reduction in maximum blood glucose reduction from 27.84% to 23.99%.

Further, the study was extended to diabetic albino rats with a single dose treatment of tolbutamide and glibenclamide in two saperate groups and prior treatment of Lamotrigine (100mg/k g) for 7 days and on 8th day 2 groups were administered with tolbutamide and glibenclamide single dose.

The tolbutamide group did not show any alteration in onset, duration of action and peak effect. The maximum reduction in blood glucose levels was from 55.50% to 48.42%. Glibenclamide anti-diabetic activity in diabetic rats also reduced due to prior treatment of Lamotrigine throughout the experimental study. The duration of action was reduced where as onset and peak effects were not

altered. The maximum blood glucose reduction was from 57.21% to 51.22%.

BIBLIOGRAPHY

1. James O Mc Namara J. Drugs effective in the treatment of the epilepsies. In pharmacological Basis of Therapeutics 10 th ed. Hardmann JG,Limbard JE,Molinoff PB,Ruddon RW,Gilmann AG, eds. New York:Mc Graw Hill;1996:521-5.
2. SatoskarRS,BhandarkarSD, AinapureeSS.PharmacologyandPharmacotherapeutics .17th ed .Mumbai: Popular prakashan;
3. Badyal DK, Dadhich AP. Cyto chrome P450 and drug Interactions. Indian Journal of Pharmacology 2001 March 10; 33:248-59.
4. Terri L Leviea, Danial E Baker. Cytochrome P 450 drug Interactions. Stockan,California: Therapeutic Research centre1 999.
5. Rohit Singhal, Nagavi BG ,Adepu Ramesh. Drug Interactions in community pharmacy. Pharma Times 2004; 36:20-26.
6. Theodora Michel .Epilepsy "The disease" The Pharmaceutical Journal, 1999 Feb 27; 262(7034): 297-300.
7. Satyanarayana S, Prasad K, Nitin K. Pharmocodynamic drug interaction of selegiline and Tolbutamide in rats. Indian drugs 2003; 40(6):366-8.
8. Vinuthan MK .et.al.Effect of extracts of Murraya koenigii leaves on the blood glucose and plasma insulin in Alloxan-induced Diabetic rats. Indian J Physiol Pharmacol 2004;48(3):3 48-52.
9. Aruna Pai, Jalal Pure SS,Patil MB,Manvi Fv, Shivaji Bamme.Antidiabetic activity of Cassia auriculata linn.seeds.55th IPC Chennai 2003:231.
10. Goyal RK, Kulkarni J, Mehta AA, Santani DD. Effects of chronic treatment with cromakalin and glibenclamide in alloxan diabetic rats. Indian Journal of Pharmacology1997; 29:36.
11. Syamala G, Subburaju T, Jhuma deb, Kumar EP, Suresh B. Anti-diabetic activity of detoxified extract Cascaria esculenta (Roxb).55th IPC Chennai 2003:254.

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