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Clinicopharmacological evaluation of drug interaction between Rifampicin and gliburide in Tuberculosis patients with Type II diabetes.

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Abstract: *In our community Diabetes Mellitus and pulmonary Tuberculosis are still very common. The % of Pulmonary Tuberculosis among diabetic patients is nearly 27% by radiological diagnosis (377J IMA vol 100NO.6 june 2002). The % of diabetes among pulmonary tuberculosis patients is 6.5%. Both diseases are chronic and co-exist not commonly. It is said that if tuberculosis is uncontrolled inspite of meticulous anti TB treatment of tuberculosis patients suspect latent diabetes. When both diseases coexist they are mutually aggravating. If they are simultaneously treated effectively the effect is good. Unfortunately TB requires polypharmacy. Some of the recent anti TB drugs like Rifampicin have enzyme inducing capacity producing a low blood level concentration of certain drugs like glibenclamide (sulphonylurea) with which it interacts. In maturity onset diabetic (NIDDM)patients with TB taking glibenclamide for the control of diabetes and Rifampicin containing regimens., simultaneously for TB it was found that the requirements of the oral hypoglycaemic agents are increased to control the diabetes[1] . It was proved that Rifampicin by inducing the cytchrome P450 enzymes in the liver interacts with glibenclamide resulting in low blood level concentration of glibenclamide with less stimulation of Beta cells of pancreas with lowered endogenous insulin production, with little hypoglycaemic effect resulting in uncontrolled hyperglycaemia. This was an established fact. So to evaluate and assess the drug interaction of Rifampicin with glibenclamide in Type II diabetes with PT patients, this study was under taken. Similar study was not done previously in this hospital.*

I. Review of Literature:

Prevalence of Diabetes – The Global Senario.

The WHO estimated that there are 135 million diabetic individuals in the year 1995 and it has projected that this number would increase to 300 million by the year 2025[2]. It also declared that Diabetes had reached epidemic proportions and predicts that most of the increase will be contributed by developing countries, particularly India[3].

Prevalence of Diabetes – The Indian scenario.

India today leads the world with its largest number of diabetic subjects in any give country[3,4.] It has been estimated that presently 19.4 million individuals are affected by diabetes and these numbers are expected to increase to 57.2 million by the year 2025[2]. (1/6 of the world total).The diabetic classification was adopted in 1980, and modified in 1985 [5,6].

In 1970's the prevalence of diabetes among urban Indians was reported to be 2.1%, this has now risen to 12.1% [7,8].

Induction of Rifampicin metabolism during treatment in TB patients with daily and fully intermittent regimens containing the drug [9,10,11,12].Self induction of Rifampicin metabolism during daily and intermittent cheamotherapy was studied by monitoring the changes in the serum half life of the drug over a week period in patients with PT. Rifampicin 450 mg was administered to 8 patients who received treatment daily, to 7 patients taking thrice weekly and 8 others on twice weekly treatment[13]. Serum half life was computed from concentrations of the drug determined at 3, 4½, and 6 hours after drug administration, on admission and at 1,2

and 4 weeks after starting of treatment. In the daily series, the mean serum half life decreased from 4.9 hours on admission to 3.6 hours at 1week (P=0.02), and treatment beyond this had no further effect[14].

In the thrice weekly series, maximal induction was observed at the 2nd week, the main values on admission and at 2weeks being 5.8 and 3.7 hours respectively. (P=0.01). In the twice weekly series maximal induction was observed only at the 4th week, the mean values on admission and at 4weeks being 4.9 and 3.7 hours respectively[15].

Rifampicin:

This appears to stimulate the metabolism of glibenclamide by hepatic microsomal enzymes. It shown to enhance considerably the disposition of glibenclamide and decreases half life and impairs hypoglycaemic response. When Rifampicin and Glibenclamide are used concomitantly one should be alert for diminished hypoglycaemic activity of Glibenclamide.

II. Aims and Objectives:

Detection of drug interaction between anti tubercular Rifampicin and oral antidiabetic Glybenclamide by Pharmacokinetic study of diabetic state. Control of both diseases simultaneously by rectifying hyperglycaemic effect of Rifampicin on control of diabetes. Comparing study group treated with HREZ and control group with HEZ to prove Rifampicin is the drug responsible for hyperglycaemia.

III. Materials and Methods:

Patients suffering from both Tuberculosis and Diabetes Mellitus type-II were selected betwin age groups 35 – 60yrs and admitted in This Hospital.The patient should be non smoker, non alcoholic with normal liver and kidney function.

A minimum of 40 such patients were randomly distributed into two groups of 20 each. Informed consent was obtained from each subject and institutional ethics committee permission was taken. Both the groups were put on 3 drug regimen (HEZ) and glibenclamide 2.5 mg Bid and the fasting glucose levels were normalized by about 5th day. Then in the study group Rifampicin 600mg to patients above 50kg and 450mg to patients below 50kg was added to the above regimen. In the control group 3drug regimen (HEZ)+ glibenclamide continued. Fasting blood glucose levels were estimated on alternate days in both the groups . The day at which the blood glucose levels increased was noted in the study group. It indicates the stage of drug interaction. After detecting the rise of blood glucose levels and there is no further increase for two days the dose of glibenclamide was increased to compensate the effect produced by drug interaction and blood glucose levels normalized in about 5days in the study group.In the control group there is no significant increase in fasting glucose levels and the same dose of glibenclamide continued.

Unpaired 't' test was used for the statistical analysis.

IV. Results

Total 40 cases of confirmed pulmonary Tuberculosis and Type II Diabetes Mellitus, who were non smokers and non alcoholics and whose diabetes is of less than 5 years duration and whose blood sugar is under control with less than 40 units of Insulin per day were selected in this study.These cases were divided into two groups of 20 each, study group and control group and studied and analyzed for pharmacological detection of drug interaction.(Table-1- control group and Table-2 –study group).

Tables:

Table - 1 (Control Group):

S. No	I.P.No.	Age (yrs)	Sex	Wt (kgs)	Fasting Blood Glucose mg/dl				Treatment
					Initial	5th Day	15th Day	20th Day	
1	156642	38	Male	55	176	106	100	104	HEZ+ glibenclamide
2	113942	42	Female	54	167	98	102	96	"
3	117819	44	Male	61	180	110	106	108	"
4	114944	46	Female	56	174	90	96	94	"
5	182418	51	Male	59	186	96	90	98	"
6	117889	54	Female	55	166	106	101	108	"
7	132526	37	Male	60	160	88	92	94	"
8	132211	52	Male	62	186	112	98	104	"
9	117427	44	Female	56	209	86	90	88	"
10	115581	41	Male	58	168	110	102	106	"

11	205531	38	Female	52	146	82	90	86	"
12	182490	55	Male	60	182	114	108	110	"
13	205702	46	Female	54	172	118	104	108	"
14	132967	48	Male	56	180	116	106	112	"
15	112735	35	Female	51	192	90	96	96	"
16	133424	53	Male	58	188	114	104	116	"
17	155797	49	Female	51	162	92	98	94	"
18	140587	46	Male	58	190	108	102	110	"
19	160742	55	Female	51	168	88	92	96	"
20	183473	40	Male	54	172	104	110	111	"
				Mean	176	101	99	102	
				SD	± 13.86	± 11.52	± 6.25	±8.53	

Table - 2 (Study Group):

S. No	I.P.No.	Age (yrs)	Sex	Wt (kgs)	Fasting Blood Glucose mg/dl				Treatment
					Initial	5th Day *R	15th Day*G	20th Day	
1	121227	42	Male	56	162	104	144	110	HEZ+ glibenclamide
2	116041	36	Female	45	154	98	132	104	"
3	130102	46	Male	52	176	108	138	106	"
4	160439	43	Female	50	180	92	140	98	"
5	122123	51	Male	54	150	112	138	114	"
6	160789	45	Female	48	178	114	145	110	"
7	121178	38	Male	60	149	96	141	102	"
8	146637	54	Male	58	186	116	120	120	"
9	157680	55	Female	51	148	90	131	94	"
10	117204	40	Male	56	164	115	145	110	"
11	141194	46	Male	53	180	110	135	108	"
12	123463	44	Female	48	181	104	142	111	"
13	183120	39	Male	54	154	98	136	105	"
14	116649	55	Female	47	158	95	132	102	"
15	156121	48	Male	61	186	111	146	116	"
16	146605	56	Female	60	172	98	136	106	"
17	157680	38	Male	57	188	116	130	114	"
18	145493	52	Female	56	141	80	126	92	"
19	144274	52	Male	62	190	112	138	114	"
20	159241	46	Female	54	148	96	131	100	"
				Mean	167	103	136	107	
				SD	± 16.02	± 10.15	± 7.14	± 7.36	

*R = Rifampicin added on 5th day
*G = Increased dose of glibencalmide on 15th day

V. Discussion

In both groups fasting blood glucose levels were taken initially and both the groups were put on Anti TB drugs H.E.Z. and glibenclamide and the Fasting blood glucose levels were normalized by about 5^{th} day . After the normal levels have reached Rifampicin was added according to body weight in the study group.

In the study group the fasting blood glucose levels were raised gradually and reaches maximum by 8^{th} day of addition of Rifampicin from 103 mg/dl to 136mg/dl. The blood sugar value was significantly raised.

In the control group there is no such rise in fasting blood glucose as found in study group. The blood sugar levels on 5^{th} day is 101mg/dl and on 15^{th} day is 102mg/dl. There is no significant difference. Comparision of raised blood glucose levels in study group and control group, There is a significant difference (P=<0.05) in both groups on 15th day of treatment i.e. 10^{th} day of start of Rifampicin therapy. The blood glucose levels were gradually increased from 5^{th} day and reaches maximum by 8^{th} day of starting of Rifampicin therapy in study group and later remained constant. From 10^{th} day the dose of glibenclamide was increased to reduce the blood glucose levels to normal.

VI. Summary:

This work is done to show the drug interaction. When so many drugs are used, the effect of one drug may inhibit the action or potency of other drugs and there by decreasing the chances of recovery from the disease. In this study we have simultaneously treated the tuberculosis with the anti TB drugs and diabetes with oral sulphonylurea. But in the study group we have added the Rifampicin which produced a diminished effect of glibenclamide due to increased metabolism by enzyme induction. So there is an increase in fasting blood glucose level, and this is controlled by increasing the dose of glibenclamide.

This hyperglycaemia may prevail the existing TB and chances of recovery is less unless the blood sugar level is within normal limits. The study of drug interaction is very important and vital particularly in therapy with potent drugs because the multiple drug therapy has come to stay in the present day clinical practice in long term treatment, to avoid resistance.

INFERENCE:

In this study in patients with glibenclamide and anti TB drugs HREZ, drug interaction was detected as raised blood glucose, on 15^{th} day (i.e. $8^{th} – 10^{th}$ day of Rifampicin therapy).

In control group patients with glibenclamide and antiTB drugs (Non Rifampicin) HEZ there was no such drug interaction. Blood glucose levels were unchanged. After drug interaction hyperglycaemia was continued in study group and it was compensated by increased dose of glibenclamide.

So in clinical practice during treating a patient having both PT and Type II diabetes mellitus , the result of the study is quiet useful to avoid hyperglycaemia.

VII. Conclusion:

In case of TB patients with diabetes mellitus Type II if we give short course chemotherapy with Rifampicin regimen you should be cautious about drug interaction. You should increase the dose of oral hypoglycaemic sulfonylurea to control diabetes and pulmonary tuberculosis.

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