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Effects of Enzyme Inducers in Therapeutic Efficacy of Rosiglitazone: An Antidiabetic Drug in Albino Rats

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Abstract : The effect of enzyme inducers on therapeutic efficacy of Rosiglitazone (an antidiabetic drug) was evaluated by using alloxan induced diabetic rats. The results exhibit the combined adminstration of enzyme inducers like rifampicin, phenobarbitone and phenytoin with Rosiglitazone was contraindicated. The purpose of the study reveals that if Rosiglitazone drug combined with said enzyme inducers then therapeutic efficacy of Rosiglitazone being altered. Because enzyme inducers induced cytochrome P450 by enhancing the rate of its synthesis and/or reducing the rate of degradation. Therefore, combined administration of enzyme inducers with Rosiglitazone is not advisable. Since the hypoglycemic effect of the drug is reduced. The results exhibit that combined administration of enzyme inducers with Rosiglitazone was contraindicated.

Key words : Rosiglitazone, alloxan, phenytoin, Rifampicin, phenobarbitone

Introduction :

Rosiglitazone an antidiabetic thiazolidine category of drugs clinically decrease insulin resistance in muscles and liver, which enhances glucose utilization and decreases hepatic glucose output with the modern approach of keeping blood sugar level under control in patients with type-II diabetes (NIDDM).

Molecular actions of these agents is known that they bind to and activate a nuclear receptor peroxisome proliferator activated receptor gamma (PPAR-) that is present in many insulin sensitive tissues.

PPAR- regulates transcription of insulin responsive genes that influence glucose and lipid metabolism.

When enzyme inducers such as phenytoin, phenobarbitone and rifampicin are taken concurrently with oral antidiabetics, the therapeutic efficacy may get altered as enzyme inducers induces cytochrome P450 by enhancing the rate of its synthesis and/or reducing the rate of degradation (Badal and Dandhich, 2001). So the present work deals with the effect of above mentioned enzyme inducers on therapeutic efficacy of Rosiglitazone.

Materials and Methods :

Swiss albino rats (150-200 gm) brought to Central Animal House (Reg.No.160/ 1999/CPCSEA) Annamalai University, Annamalai nagar, Tamilnadu were used throughout the study. Animal were housed in

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an airconditioned room at 24º. The animals were treated with 100 mg/kg of alloxan monohydrate in normal saline. The rats which showed blood glucose level more than 140 mg% 20 days after injection of alloxan were included in the study. Animal were divided into following group, each group have 6 animals.

Group A - Normal Control

Group B - Diabetic Control

Group C - Rosiglitazone Control

Group D - Rosiglitazone (2mg/kg) + Rifampicin (10 mg/kg)

Group E - Rosiglitazone (2mg/kg) + Phenobarbitone (20mg/kg)

Group F - Rosiglitazone (2mg/kg) + Phenytoin (25 mg/kg)

All the above enzyme inducers such as phenytoin, phenobarbitone and rifampicin (Atlas E. and Turck, M.1968; Young et. al., 2004) were mixed with rosiglitazone powdered drug and given orally by gastric tube, a sample of blood was withdrawn by retro-orbital puncture just prior to administration of drug and also at periodical intervals upto three hours. The blood glucose level, creatinine level and H.D.L. cholesterol level have been determined by Autoanalyzer (Allain et. al., 1974).

Result and Discussion :

According to graphical representation (Fig. 1 and 2) and tabulated value's (Table 1 and 2) it has been depicted that rosiglitizone - a standard antidiabetic drug when given orally to diabetic rat's, 20 days after producing diabetics by alloxan, showed decreased blood glucose level from 17% to 45% within the period of 2.5 hrs.

Rifampicin, Phenobarbitone and Phenytion the common enzyme inducer's when given with rosiglitazone separately to the same diabetic rat's, the effect of rosiglitazone was found to be reduced (Young *et. al.*, 2004; Perucca , 1982; Raj Kapoor and Kavimani, 2004).

Blood glucose level was reduced from 17% to 8%, 7%, 8% and 45% to 36%, 35%, 33% from period of 2.5 hrs. When rifamipicin, phenobarbitone, phenytoin were give to rat's along with rosiglitazone respectively.

Result shown that rosiglitazone drug combined with enzyme inducers such as rifampicin, phenobarbitone and phenytoin lowered the therapeutic efficacy of rosiglitazone. Because enzyme induer's induced cytochrome P450 by enhancing the rate of its synthesis and/or reducing the rate of degradation (Badal D. K.and Dandhich A. P., 2001).

Therefore combined administration of enzyme inducers with rosiglitazone is not advisable. Since the hypoglycemic effect of the drug is reduced (Young et. al., 2004).

Summary and Conclusion :

The effect of enzyme inducer's in therapeutic efficacy of rosiglitazone, shown that rosilitazone induced the hypoglycemia by increases skeletal muscles cells sensitivity to insulin and decrease hepatic glucose production.

Since combined administration of rosiglitazone with three different enzyme inducer's alter the therapeutic efficacy of rosiglitazone due to induction of cytochrome P450 microsomal enzyme by enhancing the rate of its degradation.

Therefore its concluded that combined administration of enzyme inducer's - rifampicin, phenobarbitone, phenytoin with rosiglitazone should be avoided.

Table 1 : The Effect of Enzyme Inducers on Blood Glucose Level

Gr. No	**Treatment**	Plasma sugar level (mg/dl)						
		Initial	0.5 hr	1.0 hr	1.5 hr	2.0 hr	2.5 hr	3.0 hr
A	Normal control	67.20±1.48	68.72±0.45	70.56±0.64	69.88±0.57	69.88±0.55	68.59±0.59	68.58±0.56
B	Diabetic control (alloxan – 100mg/kg i.p)	149.33±0.71	149.50±0.67	150.66±0.80	151.83±1.49	150.5±0.71	149.83±0.47	151.0±0.89
C	Rosiglitazone control (2 mg/kg p.o)	148.5±0.67	N.S 124.33±0.49	d 114.50±1.05	c 106.66±0.55	d 100.16±0.47	b 89.5±0.42	b 79.33±0.61
D	Rosiglitazone + Rifampicin (2 mg/kg p.o) (10 mg/kg p.o)	149.33±0.71	d 136.16±2.75	c 129.50±2.89	N.S 119.66±2.40	d 111.0±2.58	b 104.83±2.12	a 96.50±0.71
E	Rosiglitazone + Phenobarbitone (2 mg/kg p.o) (20 mg/kg p.o)	148.66±0.9	c 139.33±0.61	d 133.50±0.92	d 127.0±0.93	N.S 119.0±0.36	a 109.5±0.56	b 97.16±0.60
F	Rosiglitazone + Phenytoin (2 mg/kg p.o) (25 mg/kg p.o)	151.0±0.81	a 139.0±0.36	b 131.5±0.56	b 124.5±1.25	c 115.5±0.95	d 107.5±0.50	N.S 100.83±0.60

Each value is the mean of 6 rat's ±S.E

a ==> $p < 0.05$ b ==> $p < 0.02$

c ==> $p < 0.01$ d ==> $p < 0.001$

N.S ==> Non- significant

Table 2 : Total Blood Cholesterol, Hdl Cholesterol And Creatinine Level (mg/dl)

Treatment	PARAMETER'S					
	Plasma total cholesterol		Plasma HDL cholesterol		**Plasma creatinine**	
	Initial	After 3 hrs	Initial	After 3 hrs	Initial	After 3 hrs
control	81.24±0.65	79.20±0.64	38.35±0.77	41.52±0.88	0.53±0.01	0.54±0.01
: control (alloxan – kg i.p)	87.25±0.71	96.71±0.46	29.73±0.54	28.37±0.48	1.31±0.02	1.28±0.01
azone control g p.o)	85.57±0.30	N.S 91.54±0.77	d 33.24±0.99	a 34.91±0.82	a 1.26±0.03	N.S 0.97±0.009
azone + Rifampicin g p.o) (10 mg/kg p.o)	84.80±0.46	c 92.58±0.83	d 31.74±0.77	N.S 33.83±0.95	d 1.26±0.01	b 1.06±0.02
azone + Phenobarbitone g p.o) (20 mg/kg p.o)	86.73±0.39	d 93.15±0.29	a 30.85±0.68	b 31.68±0.77	a 1.28±0.01	c 1.08±0.03
azone + Phenytoin g p.o) (25 mg/kg p.o)	86.70±0.6	d 91.20±0.68	a 30.35±0.63	b 34.29±0.31	a 1.27±0.009	c 1.07±0.03

Each value is the mean of 6 rat's ±S.E
a ==> $p < 0.05$ b ==> $p < 0.02$
c==> $p < 0.01$ d ==> $p< 0.001$
N.S ==> Non- significant

Fig. 1 : The effect of rosiglitazone with ezyme inducers on hyperglycaemic rats

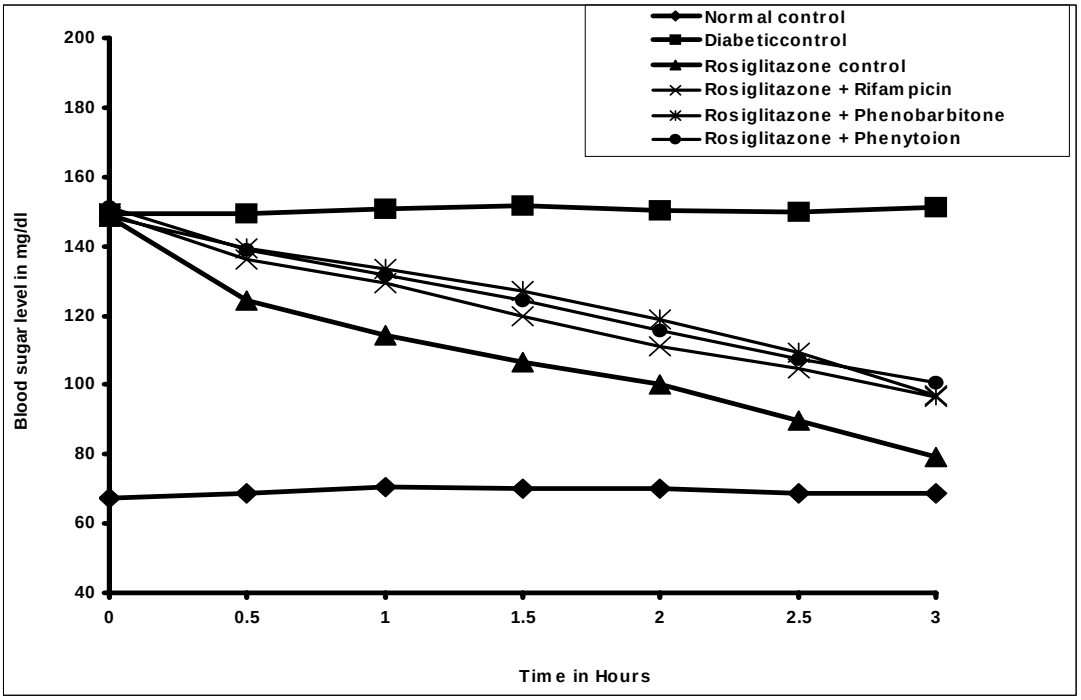
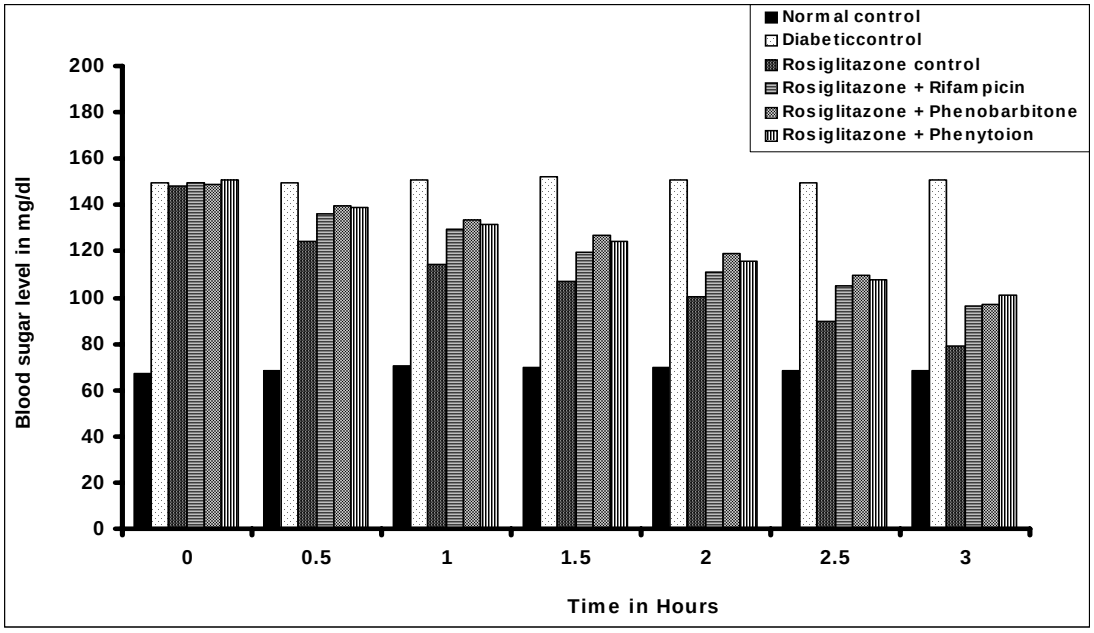


Fig. 2 : The effect of rosiglitazone with ezyme inducers on hyperglycaemic rats



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