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ORIGINAL ARTICLE

Influence of esomeprazole on the pharmacodynamic activity of thiazolidinediones (pioglitazone and rosiglitazone) in animal models

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Abstract

Drug-drug interaction studies are essential building blocks in drug development. Thiazolidinediones (TZDs: pioglitazone, and rosiglitazone) are peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, which have been widely used in the treatment of type 2 diabetes as insulin sensitizers. Esomeprazole, the (*S*) -isomer of omeprazole, is the first proton pump inhibitor (PPI) developed as a single isomer for the treatment of acid-peptic disease by specific inhibition of H^+K^+- ATPase in gastric parietal cells. The role of esomeprazole on the pharmacodynamic activity of TZDs is not currently known; however, there is the possibility of drug interaction (DI) leading to decreased activity of TZDs. The study was planned to investigate the safety and effectiveness of TZDs therapy in the presence of esomeprazole in animal models.

Key words

esomeprazole, pioglitazone, radioimmunoassay

INTRODUCTION

Gastric pathology is a common complication of diabetes mellitus (DM). The Study of the mechanisms of drug interaction is valuable when selecting the drug concentrations that provide rational therapy. The drug interaction studies assume much importance for drugs that have a narrow margin of safety or where the drugs are used for prolonged periods of time. Drug interactions played a vital role in reported adverse events, and the majority of drugs withdrawn for safety reasons from the US market were related with significant drug-drug interactions. The importance of this fact is further emphasized by an increased postmarketing adverse event reports by 240% during the last decade [1].

Management of type 2 diabetes mellitus usually involves combined pharmacological therapy to obtain adequate blood glucose control and treatment of concurrent pathology associated with it. DM increased the mucosal susceptibility to ulcerogenic stimuli and predisposition to gastric ulceration. However, incidences of gastric ulcer in diabetes may be infrequent, gastric bleeding is often fatal in diabetes [2]. Prolonged diabetic conditions have a deleterious influence of the gastrointestinal tract and maintenance of normal blood glucose level is very important in this condition, since both hypoglycaemia, as well as hyperglycaemia, is an unwanted phenomenon. Many diabetic patients develop multiple pathologies, such as hypertension, peptic ulcer (PU), etc. PU is a complication commonly seen in chronic diabetes. An estimated 15,000 deaths occur each year as a consequence of PU and 7% of diabetic patients suffer from peptic ulcer [3]. Hence, with oral hypoglycaemic drugs, the addition of drugs used to treat peptic ulcer is necessary in these patients.

It is of importance to propose therapeutic strategies with fewer side-effects, such as the use of PPIs, and this approach appears to be successful in controlling gastric complications. In this context, there are more chances of co-administration of PPI with TZDIs in patients with concurrent type 2 diabetes mellitus and gastric complication, which may lead to potent drug-drug interactions. However, there is little information is available which could elucidate the mechanisms of drug interactions between PPI and TZDIs, essential to clinicians to prescribe the rational drug combinations with respect to safety and efficacy.

The study of metabolic abnormalities in animal models contributes importantly to advances in our understanding of the physiology and pathophysiology of blood glucose, insulin resistance, β-cell function in gastric complication and diabetes.The diagnosis, as well as the progression/ remission of DM, is usually based on the evaluation of biochemical parameters *viz*., blood glucose, plasma insulin, insulin resistance and β-cell function levels. In type 2 DM, regulation of glucose metabolism is a key aspect of metabolic homeostasis, and insulin is the predominant hormone influencing this regulatory system. Insulin plays a key role in the maintenance of glucose homeostasis and is the major modulator of glucose storage and utilization. In this study, glucose was measured as a metabolic control of insulin action. The impairment of glucose homeostasis and increase in plasma glucose levels is associated with diabetes. Insulin resistance is a state where normal or elevated insulin level produces a reduced biological response, and refers to impaired sensitivity to insulin-mediated glucose disposal.

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Therefore, it is of the utmost importance to investigate glucose–insulin homeostasis, in order to better understand the pathological process of insulin resistance to evaluate the safety and effectiveness of drug combinations. The homeostasis model assessment (HOMA) is a more reliable and validated method to measure insulin resistance and β-cell function from fasting glucose and insulin [4].

TZDIs is a treatment for 2 DM, it acts as an insulin sensitizer that enhances sensitivity to insulin in the liver, fatty tissue and striated muscle. It also decreases hepatic glucose production and increases its peripheral consumption [5]. Proton pump inhibitors (PPIs) have demonstrated an excellent safety profile, even after approximately two decades of clinical use [6]. Esomeprazole acts directly by inhibiting the exchange of (H^+, K^+ -ATP) across the apical plasma membrane of the parietal cells of the gastric mucosa, and inhibit gastric acid secretion [7, 8, 9]. Hence, the study was designed to establish the safety and effectiveness of the drug combination in animal models with respect to blood glucose, insulin, insulin resistance and β-cell function, and to discover the mechanisms responsible for the interaction, if any.

MATERIALS AND METHOD

Esomeprazole and pioglitazone were obtained from Aarti Drugs, Ltd., and Aurochem Pharmaceutical Ltd (Mumbai, India) and rosiglitazone obtained from Micro Labs, (Bangalore, India), respectively. Alloxan monohydrate was purchased from Sigma Chem. (Mumbai, India). Glucose Kits (Span Diagnostics Udhna, India) were purchased from a local pharmacy. All other reagents/chemicals used were of analytical grade.

Animals. Albino rats of both genders, aged 6 – 7 weeks, weighing between 200–300g, and normal albino rabbits of both genders, aged 3 – 5 months, weighing between 1.40–1.80kg, were used in the study. They were procured from the HSK College of Pharmacy in Bagalkot and Karnataka, India. The rats were maintained under standard laboratory conditions at an ambient temperature of 25 ± 2 °C and 50 ± 15% relative humidity with a 12h light/12h dark cycle. Animals were fed with a standard pellet diet (AmruthPvt Ltd., Sangali, and Maharashtra, India) and water *ad libitum*. They were fasted for 18h prior to the experiment, and during the experiment food and water were withdrawn.

The animal experiments were performed after prior approval of the study protocol by the Institutional Animal Ethics Committee and by the Government regulatory body for animal research. (IAEC/ HSKCP/07–08). The study was conducted in accordance with the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Dose and drug administration. In clinical practice, esomeprazole and TZDIs in a therapeutic dose is administered orally. Hence, human oral therapeutic doses of the respective drugs were extrapolated to rat/rabbit, based on body surface area [10]. The dose of pioglitazone for the rat experiments was selected as 10 mg/kg bodyweight, based on the influence of the dose-effect relationship of pioglitazone on blood glucose in normal rats. Esomeprazole and TZDIs were suspended in 2% acacia suspension for oral administration [11].

Experimental plan. The study consists of three phases:
Phase I – interaction study between esomeprazole and TZDIs in normal rats.
Phase II – interaction study between esomeprazole and TZDIs in diabetic rats.
Phase III – interaction study between esomeprazole and TZDIs in normal rabbits.

Pharmacodynamic interaction studies in normal rats. Albino rats were divided into 3 groups of 6 animals each. The animals were fasted for a period of 18h prior to the experimentand water supplied *ad libitum*. Group I served as control and received a 2% acacia suspension, group II received esomeprazole 3.6 mg/kg, goup III received 10 mg/kg ofpioglitazone, group IV received 720μg/kg of rosiglitazone orally. One week washout period was maintained between treatments. In the next phase, groups III and IV received esomeprazole 3.6 mg/kg/day for 7 days. On the seventh day, 6h after esomeprazole administration, the animals were fasted for 18h but water available *ad libitum*. On the eighth day, 1h after esomeprazole and acacia suspension administration, the animals received pioglitazone 10 mg/kg and rosiglitazone of 720μg/kg.

Pharmacodynamic interaction studies in diabetic rats. Experimental diabetes was induced in rats by the injecting of alloxan monohydrateintraperitonially at a single dose of 120 mg/kg in ice-cold normal saline [14, 15]. After 72h, samples were collected from all surviving rats by orbital puncture before the blood glucose level was determined. Rats with blood glucose levels of 200 mg/dL and above were considered as diabetic and selected for the study. Animals were maintained for 4 days in a diabetic condition for well establishment of diabetes. The same protocol as described in the study in normal rats was performed with a group of 6 alloxan-induced diabetic rats. For insulin estimation, the serum was separated by centrifugation and sent to the RIA laboratory in Belgaum, India, for examination of insulin by radioimmunoassay on a fully automated 12-well multi-gamma counter radioimmunoassay system using ^{125}I (PC RIA MAS, Strategy, Germany). The results of insulin were expressed as micro-international units/ml (μIU/ml) [13, 14].

Determination of insulin resistance index and β-cell function. The insulin resistance index and β-cell function were assessed by the HOMA protocol and calculated as follows: [4, 16]

$$\text{Insulin resistance} = (\text{FPI} \times \text{FPG}) / 22.5$$

$$\beta\text{-cell function} = (20 \times \text{FPI}) / (\text{FPG} - 3.5)$$

whereas, FPI is fasting plasma insulin concentration (μu/ml) and FPG is fasting plasma glucose (mmol/L).

Pharmacodynamic study in rabbits. The animals were divided into 3 groups of 5 animals each. The animals were fasted for a period of 18h prior to experimentation and water supplied *ad libitum*. Group I served as control and received a 2% acacia suspension, group II received pioglitazone 10 mg/kg, group III received rosiglitazone of 720μg/kg**.** A **o**ne-week washout period was maintained between treatments. In the next phase, the same group was continued with the daily treatment of interacting drug (esomeprazole 1.8 mg/kg) for the next 7 days, with regular feeding. On the seventh day, 6h after esomeprazole administration, the animals were fasted

for 18h and water provided *ad libitum*. On the eighth day, 1h after esomeprazole, the animals received pioglitazone 10 mg/kg and rosiglitazone of 720μg/kg.

Blood sample collection. Blood samples were withdrawn from the retro orbital plexus [12] of each rat at 0, 1, 2, 4, 8,12,18 and 24h. Blood samples were withdrawn from the marginal ear vein of each rabbit at 0, 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24h. The blood samples were analyzed for blood glucose by the GOD/POD method [13, 14] using commercial glucose kits; plasma insulin was measured by the RadioImmuno Assay method.

Data and statistical analysis. Data were expressed as mean ± SEM. Significance was determined by applying Student's paired *t* test.

RESULTS

Pharmacodynamic interaction study in pioglitazone with esomeprazole. Pioglitazone produced hypoglycaemic activity with a maximum reduction of 51.93±2.19% and 8h, respectively, in normal rats (Tab. 1). Pioglitazone produced anti-hyperglycaemic activity with a reduction of 46.66±1.40% at 8h, respectively, in diabetic rats (Tab. 1). Pioglitazone produced hypoglycaemic activity with maximum reduction of 36.10±2.06% at 12h in normal rabbits (Tab. 3). Esomeprazole alone did not have any significant effect on the blood glucose level of rats (Tab. 1, 2, 3). In combination, esomeprazole reduced the pioglitazone activity in rats and rabbits, and the reduction was more significant with treatment of esomeprazole alone than in combination dose treatment (Tab. 1).

Pharmacodynamic interaction study in rosiglitazone with esomeprazole. Rosiglitazone produced hypoglycemic activity with maximum reduction of 47.95±3.19% and 8h, respectively, in normal rats (Tab. 4). Rosiglitazone produced anti-hyperglycaemic activity with reduction of 54.32±2.23% at 8h, respectively, in diabetic rats (Tab. 4). Rosiglitazone produced hypoglycaemic activity with maximum reduction 43.34±3.39% at 8h in normal rabbits (Tab. 4). Esomeprazole alone did not have any significant effect on the blood glucose level of rats (Tab. 4). In combination, esomeprazole reduced the rosiglitazone activity in rats and rabbits, and the reduction was more significant with treatment of esomeprazole alone than in combination dose treatment (Tab. 4).

Table 2. Mean percent blood glucose reduction in normal rabbits (N = 5)

NORMAL RABBITS			
Time (h)	Control	Pioglitazone	Pioglitazone+ Esomeprazole
0	**0**	**0**	**0**
1	0.43±0.76	7.54±0.44	9.02±1.18
2	0.10±1.01	21.55±1.41	21.57±0.66
4	2.53±1.11	23.24±3.21	32.16±2.03
8	1.78±0.41	26.93±3.72	36.07±2.06
12	0.23±1.06	36.10±2.06	40.21±1.13*
18	2.04±1.01	22.72±2.28	29.30±2.05*
24	0.93±0.74	8.41±1.62	18.27±2.42*

* Significant at P< 0.05; compared to pioglitazone control (normal rabbits).

Effect of esomeprazole on the activity of pioglitazone (blood glucose, insulin, insulin resistance index and β-cell function) in diabetic rats. Insulin plays an important role in regulating the blood glucose levels in diabetes. The average levels of blood glucose, insulin, insulin resistance and β-cell function following pioglitazone, esomeprazole and their combination at zero hour, peak hour (4h, 8h) and at the terminal stage of drug elimination (12h) are shown in Table 5. When given in combination, esomeprazole significantly (P <0.05; P <0.001; P <0.0001), altered the pharmacodynamic of pioglitazone in diabetic rats. This is reflected by a significant decrease in glucose, and an increase in insulin and β-cell function. The reduction in pioglitazone effect is greater with the combination dose treatment of esomeprazole than the dose treatment alone.

Effect of esomeprazole on the activity of rosiglitazone (blood glucose, insulin, insulin resistance index and β-cell function) in diabetic rats. In the case of rosiglitanzone studies, the average levels of blood glucose, insulin, insulin resistance and β-cell function following rosiglitazone, esomeprazole and their combination at zero hour, peak hour (4h, 8h), and at the terminal stage of drug elimination

Table 1. Mean percent blood glucose reduction in normal and diabetic rats (N = 6)

	NORMAL RAT				DIABETIC RAT		
Time (h)	C	E	P	P+E	C	P	P+E
0	0	0	0	0	0	0	0
1	3.79±0.57	3.07±0.99	8.24±1.46	3.75±1.80	0.44±0.26	14.85±2.25	12.94±1.41
2	4.41±0.89	1.40±1.58	19.98±3.29	14.77±1.82	-0.10±1.07	26.17±4.05	27.93±4.24
4	2.46±1.14	0.47±1.35	33.62±1.74	23.62±3.30**	0.49±1.00	39.26±3.63	48.93±2.43*
8	1.52±1.54	1.10±1.40	51.93±2.19	37.37±2.65*	3.33±1.07	46.66±1.40	56.63±2.34*
12	3.19±1.24	3.91±0.88	40.61±3.19	31.03±2.42**	4.13±0.60	31.70±3.04	50.85±1.90**
18	1.28±0.90	1.24±1.23	30.04±2.61	19.96±3.57*	5.45±0.22	29.78±2.40	38.43±3.53*
24	2.45±0.63	1.90±0.95	22.58±4.33	10.87±1.76*	5.96±0.53	17.20±4.60	31.74±1.78**

C – control-2% acacia suspension; E – esomeprazole-3.6 mg/kg bd.wt.treated group; P – pioglitazone-10mg/kg bd.wt.treated group; P – pioglitazone +esomeprazole
** Significant at P<0.01; * significant at P< 0.05; compared to pioglitazone control (normal rats).
** Significant at P<0.01; * significant at P< 0.05; compared to pioglitazone control (diabetic rats)

Table 3. Mean percent blood glucose reduction in normal and diabetic rats (N = 6).

	NORMAL RAT				DIABETIC RAT		
Time (h)	C	E	R	R+E	C	R	R+E
0	0	0	0	0	0	0	0
1	4.96±1.05	0.99±2.16	8.06±2.50	6.31±1.99	--1.1±1.00	7.65±0.88	4.75±3.35
2	2.05±2.51	-0.55±2.34	18.71±3.26	18.84±3.28	-0.93±1.04	19.74±3.04	16.94±4.61
4	0.25±2.71	-2.21±0.71	36.84±3.94	27.38±3.16	0.11±1.00	44.48±3.53	32.09±4.32*
8	-1.03±2.04	-1.16±1.68	47.95±3.19	34.09±2.31**	0.45±1.07	54.32±2.23	40.91±2.62*
12	1.14±2.13	4.16±1.02	24.55±3.32	16.58±2.24*	0.67±0.73	49.74±2.27	28.99±3.85***
18	0.86±1.73	3.52±1.88	13.81±3.00	3.27±0.88*	0.96±0.75	37.38±3.56	19.92±3.42**
24	-0.37±2.44	3.47±1.90	8.41±1.68	1.48±0.38*	2.7±0.54	32.70±3.52	13.95±3.04**

C – control-2% acacia suspension; E – esomeprazole-3.6 mg/kg bd.wt.treated group; R – rosiglitazone-720µg/kg bd.wt.treated group; R+E – rosiglitazone +esomeprazole
** Significant at P<0.01; * significant at P< 0.05; compared to pioglitazone control (normal rats)
** Significant at P<0.01; * significant at P< 0.05; compared to pioglitazone control (diabetic rats)

Table 4. Mean percent blood glucose reduction in normal rabbits (N = 5)

	NORMAL RABBITS		
Time (h)	Control	Rosiglitazone	Rosiglitazone +Esomeprazole
0	0	0	0
1	-3.31±1.43	8.24±0.92	3.27±1.44*
2	-0.93±1.42	23.81±0.56	18.26±2.85
4	0.05±2.75	33.64±1.90	28.16±2.36
8	2.72±1.38	43.34±3.39	41.03±3.91
12	2.06±0.83	23.30±2.41	19.69±1.99
18	0.16±2.39	17.76±2.03	4.60±1.06**
24	0.31±0.89	6.16±2.25	2.10±1.06

** Significant at P<0.01; * significant at P< 0.05; compared to pioglitazone control (normal rabbits).

(12h), are shown in Table 6. When given in combination, esomeprazole significantly altered (P <0.05; P <0.001; P <0.0001) the pharmacodynamic of rosiglitazone in diabetic rats. This is reflected by a significant decrease in glucose, and an increase in insulin and β-cell function. The reduction in rosiglitazone effect is greater with the combination dose treatment of esomeprazole than the dose treatment alone.

DISCUSSION AND CONCLUSIONS

The practice of prescribing several drugs simultaneously is common. Thus, an awareness of possible drug-drug interaction is essential to avoid catastrophic synergistic, chemical and enzymic effect that may produce toxic side-effects [16]. The mechanisms of interactions are usually evaluated in animal models, and TZDIs with statistical methodology standards similar to those used in human clinical trials [17]. Drug interactions are commonly seen in clinical practice and the mechanisms of interactions are usually evaluated in animal models (rodents and non-rodents). The presented study investigated the influence of esomeprazole on the activity of TZDIs in rats (normal and diabetic) and rabbits. The normal rat model served to quickly identify the interaction, and the diabetic rat model served to validate the same response in the actually used condition of the drug. The rabbit model is another dissimilar species to validate the occurrence of the interaction. The insulin produced by regenerated beta cells exhibited an anti hyperglycaemic response due to increased sensitization of the insulin receptors by pioglitazone. 4-hydroxyisoleucine is one of the most potent insulnotropic agents. 4-hydrooxyisoleucine increased glucose induced insulin release through a direct effect on the isolated islets of Langerhans in both rats and humans. This pattern of insulin secretion was biphasic, glucose-dependent, occurred in the absence of any change in pancreatic alpha and delta cell activity, and without interaction with other agonists of insulin secretion [18, 19].This may be the possible reason for the pharmacodynamicpotentiation of blood glucose reduction.

Although it remains unclear whether, TZDs such as rosiglitazone affect β-cell mass via direct mechanisms, there are reports suggesting that TZDs also preserve β -cell mass [20]. It is has been reported that rosiglitazone has direct effects on β cell gene expression, and that these agents may play a previously unrecognized role in the direct regulation of pancreatic β -cell function [21]. Rosiglitazone also induces recovery of pancreas β -cell function [22].

However, the presented study investigated the effect of esomeprazole on the activity of TZDIs with respect to glucose, insulin, insulin resistance and β-cell function using HOMA, which is believed to be a more reliable and validated surrogate measure [23].TZDIs produced hypoglycaemia/ anti-hyperglycaemia in normal/diabetic rats, esomeprazole is metabolized by hepatic P450 CYP2C8, CYP2C9 and CYP3A4 [24] and there is more possibility for esomeprazole to inhibit metabolism of TZIDs, which is metabolized by CYP 3A4 and CYP 2C9 [25]. Furthermore, the presence of interaction was supported by an increase in serum insulin levels with esomeprazole treatment. This needs to be confirmed by further pharmacokinetic interaction studies. The concomitant administration of esomeprazole with pioglitazone resulted in synergistic antihyperglycemic effect. Increased insulin secretion or increased glucose threshold or regeneration of pancreatic beta cells may be involved in the anti-hyperglycaemic effect. Careful designing of the timing of administration of TZDIs is important in obtaining the synergistic effect with esomeprazole.

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