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Research Article

Influence of Etoricoxib on Pharmacokinetics and Pharmacodynamics of Glibenclamide in Rabbits

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Abstract: The study was carried out to find the pharmacokinetic and pharmacodynamic drug interactions of Etoricoxib, a prototype drug used to treat chronic pain and inflammatory conditions with Glibenclamide, one of the most widely used hypoglycemic in healthy albino rabbit following single dose treatment. Glibenclamide (0.9mg/kg) and etoricoxib (5.6 mg/kg) were administered to the animals. Serum glucose levels were estimated by GOD/POD method and the influence of etoricoxib on plasma glibenclamide concentrations was determined with the help of a sensitive RP-HPLC. Rabbits were treated with both glibenclamide and etoricoxib, there was an increase in the level of plasma glibenclamide concentration and a significant reduction of blood glucose level when compared to the glibenclamide (single therapy) treated rabbits. This is the first study that provides data correlating the effects of a selective COX-2 inhibitor to the enhanced hypoglycemic effects of glibenclamide. Peak serum concentrations of glibenclamide showed considerable increments along with the potentiation of its hypoglycemic effect on concomitant use of etoricoxib. These results could be useful in the clinical evaluation of drug-drug interactions and suggests cautious simultaneous use of the two drugs-etoricoxib and glibenclamide.

Keywords: Etoricoxib, glibenclamide, pharmacokinetics, pharmacodynamics, RP-HPLC, hypoglycemia.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly efficient in the management of pain and inflammation and are an extensively prescribed class of drugs worldwide. It is estimated that about 70% of people (>65 years old) take at least one dose of NSAID each week (Talley *et al.*, 1995). An oral administration of Etoricoxib, a COX-2-selective NSAID (Dallob *et al.*, 2003) that exhibits potent analgesic and anti-inflammatory properties (Chen *et al.*, 2008) has shown to have clinical efficacy in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other inflammatory conditions(Brooks & Kubler, 2006; Siddiqui, 2009). Cytochrome P450 (CYP) 3A4 has been reported to be responsible for 40–90% of the metabolism of etoricoxib along with an involvement of other CYPs including CYP2D6, CYP2C9, CYP1A2 and CYP2C19(Kassahun *et al.*, 2001). COX-2 selective NSAIDs along with other therapies have been widely used by patients with co-morbid conditions. Thus, it is crucial to evaluate the possible pharmacokinetic interactions of etoricoxib with commonly prescribed medications.

Etoricoxib, like the other selective NSAIDs is able to impair prostaglandin synthesis by inhibiting cyclooxygenase, more particularly COX-2 in both the injured tissues and the central nervous system (Patrignani, Capone, & Tacconelli, 2003; Renner *et al.*, 2012). Also, COX-2 inhibitors have been found to be localized mainly in the insulin producing β- cells of the pancreas (Fujita *et al.*, 2007).

Furthermore, it has been estimated that by the year 2030 the number of people (>64 years) with diabetes will reach >82 million in developing countries and >48 million in developed countries which indicates the increase in the prevalence of diabetes with age (Wild, Roglic, Green, Sicree, & King, 2004). Sulfonylurea is the drug of choice for the treatment of

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type II diabetes. Glibenclamide, a second-generation sulfonylurea, increases insulin secretion by blocking the K^+-ATP channel in the pancreatic β cells (Coppack, Lant, McIntosh, & Rodgers, 1990). Glibenclamide induces insulin release and augments tissue usage of glucose at cellular level which helps in bringing down the blood glucose level. In-vitro experiments showed that glibenclamide is metabolized by CYP2C9, 2C19 and 3A4. However, the relative contributions of each CYP to the overall metabolism of glibenclamide has not been described (Van Giersbergen, Treiber, Clozel, Bodin, & Dingemanse, 2002). Glibenclamide also uses the same CYP isoforms CYP3A4, CYP2C8 and CYP2C9 as etoricoxib does for its metabolism (Yin, Tomlinson, & Chow, 2005).

Drug interactions bring about changes in the effect of one drug when administered with another. The interaction between drugs may be pharmacokinetic and/or pharmacodynamic. The effect may be an increment or a reduction in the activity and/or bioavailability of either drug. In this study, the possible interaction between two drugs of different classes used to treat two different pathophysiological conditions like diabetes mellitus and osteoarthritis/ rheumatic arthritis has been investigated. The patients suffering from diabetes mellitus, typically the elderly or mid-aged people are prone to osteoarthritis/ rheumatic arthritis (Berenbaum, 2011; Rahman, Cibere, Anis, Goldsmith, & Kopec, 2014). In such cases glibenclamide and etoricoxib are the two most frequently used drugs. However, any pharmacokinetic and pharmacodynamic changes upon interaction between the ATP-sensitive K^+ channel inhibitor, glibenclamide and etoricoxib is yet to be reported. Therefore, the present study is designed to investigate whether etoricoxib has the capacity to change the pharmacokinetics and pharmacodynamics of glibenclamide on concomitant oral administration in healthy rabbit.

MATERIALS AND METHODS

Animals

Ten randomly selected healthy New Zealand white rabbits weighing between 1.5 kg and 2.5 kg were included in our study. These rabbits were kept under standard animal house conditions of 12/12 hours day-night cycle at a temperature 25 ± 3°C and humidity 60 ± 3%. The animals were allowed to access water, ad libitum and standard food. The animals were kept in fasting condition for 18 hours prior to experimentation, but allowed free access to water. The blood samples were drawn through marginal ear vein as painlessly as possible in the welfare of animals. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) prior to start the animal experiment.

Drugs

Glibenclamide and etoricoxib were the drugs used in this study. The bulk powder form of drugs was dissolved in 2% gum acacia prior to administration.

Study Design

A parallel study was used. Total number of rabbits were divided into four groups of which, each group comprised of five animals. Animals were acclimatized in standard laboratory conditions one week prior to the experiment.

Group-I Control Group

Five rabbits were administered vehicle orally on the experimental day using an oro-gastric tube. The blood samples (1 ml) was collected just prior to administration of vehicle at 0 hour and then at 1, 2, 4, 6, 12 and 24 hours after drug administration.

Group-II Glibenclamide group

Five rabbits were administered glibenclamide, orally at a dose of 0.9 mg/kg on the experimental day using an oro-gastric tube. The blood samples (1 ml) was collected prior to glibenclamide administration at 0 h and then at 1, 2, 4, 6, 12 and 24 h after drug administration.

Group-III Etoricoxib group

Five rabbits were administered Etoricoxib, orally at a dose of 5.6 mg/kg body weight, on the experimental day using an oro-gastric tube. The blood samples (1 ml) was collected just before administration of etoricoxib at 0 h and then at 1, 2, 4, 6, 12 and 24 h after drug administration.

Group-IV Glibenclamide and etoricoxib group

Five rabbits were administered glibenclamide and etoricoxib orally at a dose of 0.9 mg/kg and 5.6 mg/kg respectively on the experimental day using an oro-gastric tube. Blood samples was drawn at similar intervals as mentioned in above groups.

All blood samples were drawn from the marginal ear vein. Each sample was collected in labelled, heparinized (20 IU/ml) test tubes and centrifuged at 3000 rpm for 10 min. Plasma-serum was separated by centrifugation and stored at –20°C. These samples were then taken for determining blood glucose levels and plasma glibenclamide concentration where the former was estimated by GOD-POD method and later by a sensitive Reverse phase high performance liquid chromatography (RP-HPLC) method respectively.

Pharmacokinetics and pharmacodynamics studies in healthy New Zealand white rabbits

Blood was withdrawn from the marginal ear vein and glucose level was estimated by the GOD–POD method. Glucose gets oxidized by the enzyme glucose oxidase (GOD) to give D-gluconic acid and 1-hydrogen peroxide. Hydrogen peroxide in presence of enzyme Peroxidase (POD) oxidizes phenol, which combines with 4-amino-antipyrine to produce red colored quinoneimine compound which was measured at 505 nm and the intensity of the color produced is

proportional to glucose concentration in the sample. A milliliter of enzymatic solution works in 10 microliters of serum.A reading was made with a spectrophotometer at 505 nm against the enzymatic solution. The Percentage blood glucose reduction at time can be calculated as

t = (A-B/A) *100

Where **A** is the O.D. of Test at time "**t**" and **B** is the O.D. of Standard at time "**t**".

Chromatographic Condition

Plasma glibenclamide concentration was determined by using validated high-performance liquid chromatography (HPLC) method. The HPLC system consisted of The Ultimate® 3000 HPLC Auto-sampler (Dionex Co.), Ultimate 3000 Series Pump (Dionex Co), and an ultimate 3000 diode array multi wavelength detector operated at 210nm. The stationary phase was a Pre-packed 18 C column (RT 250 - 4.6 mm; particle size 5 µm). The mobile phase used was acetonitrile: methanol: 0.1 % orthophosphoric acid (pH 5.4) ratio of 50:30:20 (v/v/v) at a flow rate of 1.0 mL/min. The method was validated and found to be linear over the concentration range of 100 ng/ml to 500 ng/ml. By using a standard deviation of Y-intercepts of regression lines, the limit of detection and limit of quantification was calculated to be 7.10 ng/ml and 21.53 ng/ml, respectively. The intra-assay and inter-assay relative standard deviation (% RSD) were 6.55 % and 3.01%, respectively. The accuracy ranged between 93% and 106% for the plasma samples.

Extraction procedure

Glibenclamide was isolated from plasma by liquid-liquid extraction method. To 0.5 ml of plasma samples/standard samples a chilled mixture of acetonitrile: methanol (1:1 V/V) was added. The tubes were vortexed for 5 minutes and then centrifuged at 13523 g for 30 minutes. Following this, the supernatant was filtered through 0.2 µm syringe filter and sonicated for 5 minutes. Then 20µl of samples were aspirated to HPLC system for assay.

Data analysis

The pharmacokinetic parameters were calculated. Peak plasma concentration (C_{max}) and time to reach the peak plasma concentration (T_{max}) were calculated from the actual plasma level data. Area under the plasma drug concentration versus time curve (AUC_{0-t}) was calculated by trapezoidal rule. Statistical analysis was done using the one-way ANOVAs to find the level of significance. SEM was used since sample size was small (n = 5); p value < 0.05 was considered statistically significant.

RESULTS

Effect of single dose glibenclamide on fasting blood glucose level in etoricoxib pre-treatment healthy New Zealand white rabbit

A significant reduction in FBG level from 107.24±9.74 mg/dl to 73.38±6.42 mg/dl **(**31.57 % reduction) in glibenclamide group (group-II) was recorded at 3 hours, but not at 1 hour. No significant reduction in FBG level was seen in animals treated with etoricoxib (group-III) and control group (group-I) at 1 and 3 hours. Whereas, there was significant reduction in FBG level from 107.84±10.74 mg/dl to 78±6.98 mg/dl at 1 hour (26.67 % reduction) and to 58.96±4.77 mg/dl (45.32% reduction) at 3 hours in glibenclamide and etoricoxib treated group (group-IV). Onset of hypoglycemia (time taken to reduce the blood-glucose level to the extent of 10%) after treating with Glibenclamide + Etoricoxib group (group-IV) was at 1 hour, but the onset of hypoglycemic action was recorded after 3 hours only in glibenclamide treated group. Whereas, no onset of hypoglycemia was recorded in control and etoricoxib treated group. Duration of hypoglycemia (duration where a minimum of 10% reduction in blood-glucose level is maintained) lasted for 24 hours in Glibenclamide + Etoricoxib group whereas, it lasted for 12 hours only in glibenclamide treated group. The results of these findings have been compiled in table No. 1 and 2 and graphically depicted in figures 1 and 2.

Table 1 Fasting blood glucose concentration (mg/dl) at different time interval

Group	Mean Glucose (mg/dl)					
	0Hr	1Hr	3Hr	6Hr	12Hr	24Hr
Control	99.84±6.32	106.08±10.98	106.6±5.84	101.96±8.32	100.74±7.26	100.8±9.03
Glibenclamide	107.24±9.74	91.76±9.58	73.38±6.42***	81.42±7.00***	91.36±6.24	101.86±8.76
Etoricoxib	94.84±5.16	87.16±8.29	88.98±4.78	90.34±5.32	91.86±4.94	94.34±6.05
Glibenclamide + Etoricoxib	107.84±10.74	78±6.98**	58.96±4.77***	65.04±6.43***	85.62±7.82*	94.68±5.90

*P<0.05, **P<0.01, ***P<0.001 when all group compared with Control group

Table 2 Percentage Blood glucose reduction at different time interval

Group	Percentage Glucose change (%)					
	0Hr	1Hr	3Hr	6Hr	12Hr	24Hr
Control	0	6.25	6.77	2.12	0.90	0.96
Glibenclamide	0	14.43	31.57	24.07	14.8	5.01
Etoricoxib	0	4.09	6.17	4.74	3.14	0.52
Glibenclamide + Etoricoxib	0	26.67	45.32	39.68	20.6	12.2

Table 3 Glibenclamide Plasma concentration (ng/ml)

Group	Glibenclamide Plasma concentration (ng/ml)					
	0 Hrs	1 Hrs	3 Hrs	6 Hrs	12Hrs	24 Hrs
Glibenclamide	0	140.83	394.94	130.66	32.48	25.24
Glibenclamide and Etoricoxib	0	146.72	401.9	141.36	41.65	29.96
$AUC_{(0\text{-}24hrs)}$	4100.35(Glibenclamide) (4461.45) Glibenclamide pretreated with etoricoxib					
T_{max}	3 hrs					
C_{max}	394.94(Glibenclamide) 401.9 (Glibenclamide pretreated with etoricoxib)					

All the experiments are performed in triplicate sample.

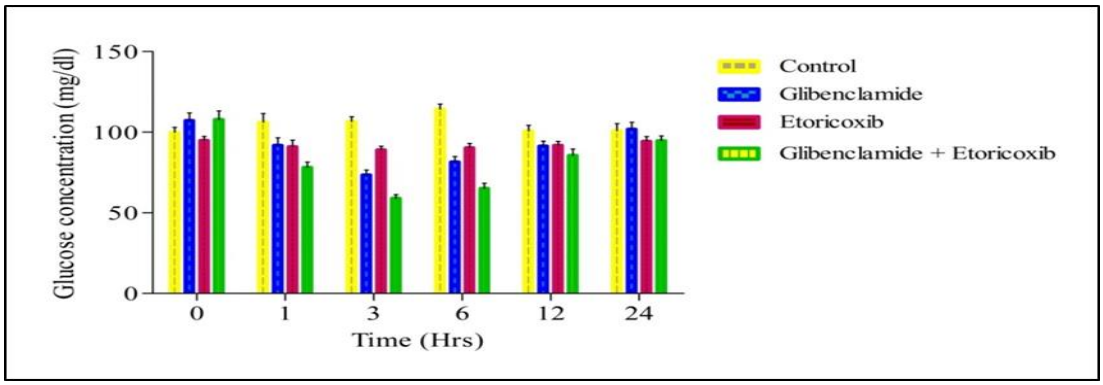

Figure 1 Fasting Glucose Concentration (mg/dl)

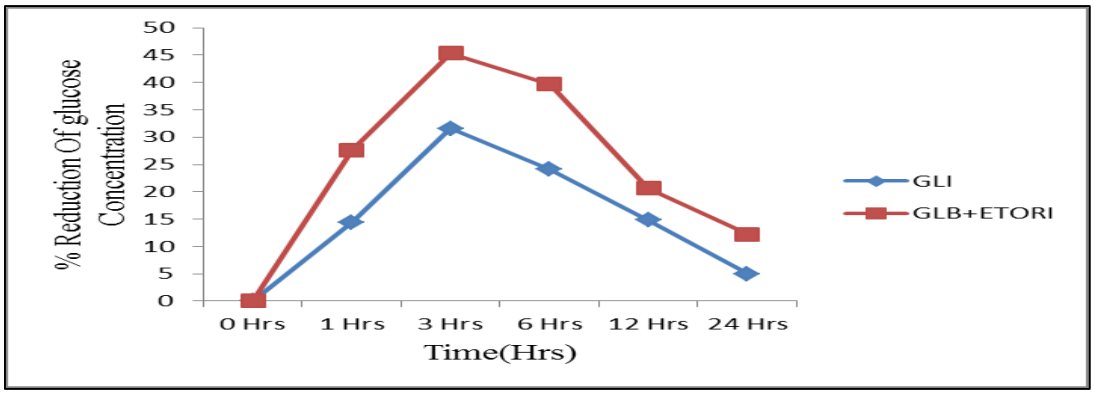

Figure 2 Percentage Blood Glucose Reduction at Different Time Interval of Glibenclamide and Glibenclamide Plus Etoricoxib

Plasma Glibenclamide Concentration Profile

In the present study, the plasma glibenclamide levels and pharmacokinetic parameters of glibenclamide like AUC, C_{max}, and T_{max} were altered on pre-treatment with etoricoxib in healthy rabbits. The average plasma concentration of glibenclamide of the animals pre-treated with etoricoxib was found to be higher than the plasma concentration of glibenclamide of normal animals treated with an oral dose of 0.9 mg/kg glibenclamide alone. Similarly, the AUC (0-24 hrs.) in the pre-treated group of animals (4461.45) was also greater than that seen in rabbits exposed only with a dose of glibenclamide (4100.35). The results have been compiled in table No. 3 and graphically shown in figure No. 3

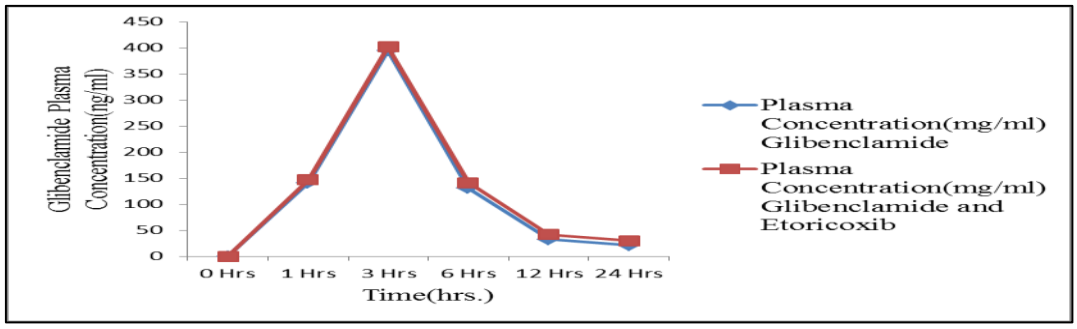

Figure 3 Glibenclamide Plasma Concentration (Ng/Ml) Respect to Time

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DISCUSSION

The most important drugs for use in type-2 diabetes mellitus are the biguanides primarily metformin and Sulfonylureas. Glibenclamide, a potent second-generation sulfonylurea, has been widely used in the management of non-insulin dependent diabetes mellitus in Europe since 1969 and in the United States since 1984. The mechanism of action of glibenclamide lies in the inhibition of ATP sensitive K+ channel which in turn improves glucose tolerance mainly by augmenting insulin secretion (Inzucchi, 2010). Etoricoxib is an NSAID, widely used in osteoarthritis, rheumatoid arthritis (Riendeau *et al.,* 2001), acute and chronic pain, migraine (Jody K. Takemoto, Jonathan K. Reynolds, Connie M. Remsberg, 2009), etc. It is a highly selective cyclooxygenase-2 (COX-2) inhibitor with anti-inflammatory and analgesic properties. Because of its COX-2 selectivity it has a lower risk of GI clinical events and is preferred for long term use as compared to traditional NSAIDs that have a higher incidence of bleeding ulcer due to the inhibition of COX-1 in the GI mucosa (Hunt *et al.,* 2003; Laine, Curtis, Cryer, Kaur, & Cannon, 2007; R.H. *et al.,* 2003). In whole blood assay etoricoxib showed 106-fold selectivity for COX-2 compared to COX-1 (Jody K. Takemoto, Jonathan K. Reynolds, Connie M. Remsberg, 2009).

In this study the possible interaction between the two different classes of drugs used to treat different pathophysiological conditions like diabetes mellitus and osteoarthritis/ rheumatic arthritis have been investigated. The patients suffering from diabetes mellitus are typically elderly or mid-aged people who are also increasingly prone to osteoarthritis/ rheumatoid arthritis (Berenbaum, 2011). In such cases sulfonylureas and NSAIDs are the two drugs most frequently used concomitantly. From the present investigation, it can be verified that the hypoglycemic effect of glibenclamide (0.9 mg/kg) increases in presence of etoricoxib (5.6 mg/kg). Our results indicate that etoricoxib does influence the pharmacodynamic properties of glibenclamide, since the onset of hypoglycemia and the peak hypoglycemic effect of glibenclamide was increased. This indicates that etoricoxib is susceptible to interfere with the pharmacodynamic profile of glibenclamide. COX-2 inhibitors are localized mainly in the insulin producing β-cells. Therefore, COX-2 inhibition is likely to influence the glucose stimulated release of insulin (Fujita *et al.,* 2007). This could be the possible mechanism for the pharmacodynamic interaction of etoricoxib and glibenclamide.

Another significant finding of this study, was the altered pharmacokinetic parameters (AUC and C_{max}) of glibenclamide in the presence of etoricoxib. Pre-treatment of the animals with etoricoxib significantly increased the AUC of glibenclamide by 8.80% along with an increase in the C_{max} (394.94 ng/ml on single treatment and 401.9 ng/ml on glibenclamide + etoricoxib dual therapy). However, no modification in the T_{max} was observed. Therefore, the results suggest that the increased plasma concentrations of glibenclamide in etoricoxib treated animals could be caused by an increase in the glibenclamide bioavailability. Etoricoxib inhibits the human cytochrome P-450 enzyme system (Kassahun *et al.,* 2001), more prominently CYP3A4 (Kassahun *et al.,* 2001; Rodrigues, 2005). In addition, our test drug glibenclamide also interacts with the same cytochrome CYP3A4 along with other isoforms (CYP2C8 and CYP2C9) (Ying Ao a, Jie Chen b, Jiang Yue a, 2008). Hence, interference of the CYP enzymes by both drugs could be the possible pharmacokinetic interaction. With this evidence, it is now possible to propose that etoricoxib also alters the pharmacokinetics of glibenclamide.

Thus, the experimental evidences obtained suggests that the concurrent use of etoricoxib with glibenclamide is most likely to enhance the hypoglycaemic effect of glibenclamide. Till date, no clinical study has been done for such interactions and thus, it such studies is necessitated in order to further ascertain the findings of this study.

One limitation of our study was the use of non-diabetic rabbits in the study. In this respect, it would be more interesting to examine the pharmacological interactions of both drugs on diabetic models.

CONCLUSION

In conclusion, our results clearly illustrate the interaction between etoricoxib and glibenclamide, as a consequence to which the hypoglycemic effect of the sulfonylurea was enhanced. Remarkable differences in the plasma concentrations of the oral hypoglycemic drug was observed when administered alone and in

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conjunction with etoricoxib. The possible mechanism of such pharmacodynamic and kinetic modulation has been hypothesized which involves the cytochromes and the regulation of insulin release by COX inhibitors. However, further studies are needed in order to understand the exact mechanism of such interactions. If similar effects are confirmed in human subjects, it would imply that cautiousness is necessary on concomitant use of the two drugs as etoricoxib could aggravate the hypoglycemic effect of glibenclamide in diabetic patients.

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