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Safety profiling of pioglitazone and telmisartan combination by sub-chronic toxicity study in rat

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ABSTRACT

It has been reported that the major cause of mortality in diabetes is cardiovascular diseases and contribution of hypertension is significant in this context. Pioglitazone, a thiazolidinedione class of therapeutic agent is used to treat type 2 diabetes mellitus. Telmisartan, an angiotensin receptor blocker antihypertensive has been reported to have beneficial effect if co-administered with pioglitazone for the management of diabetes complications. The present research work aims to evaluate the safety/toxicity profile of this combination in rat model. The investigation was carried out after co-administering the drugs to the rats for 28 days at three dose levels of 50, 100 and 150 mg/kg covering low to high dose ranges. Various hematological and biochemical parameters were studied in addition to the histopathology of the major organs in order to evaluate the toxicity profile of the combination. Absence of mortality and histopathological changes as well as unaltered hematological and biochemical parameters was observed. This preliminary investigation concludes that the combination of pioglitazone and telmisartan can primarily be stated as safe in animals, even at the dose level which is several folds higher than the intended human dose. Thus, this combination can be explored in future to develop a rational therapy regimen to treat hypertensive diabetic patients.

1. Introduction

Presently, the worldwide prevalence of diabetes mellitus is becoming alarming and it is considered as one of the major causes of mortality affecting almost all age groups (Varalakshmi et al., 2014). Surprisingly, it is very rare nowadays that type-2 diabetes mellitus patient is free from mild to moderate level of hypertension. Literature review reveals that the major health problems associated with a pathophysiological mechanism for arterial damage in diabetes is hypertension (Parameshappa et al., 2010). The co-existence of hypertension and diabetes affects the same major organs and results in left ventricular hypertrophy, coronary artery disease, decreased renal function, development of diabetic retinopathy and several cerebral diseases (Parameshappa et al., 2010). The major factors for the development of hypertension in type-2 diabetic patients are nephropathy and insulin resistance. Raised insulin levels in diabetic patient increase sodium retention and promote re-absorption of sodium and glucose. Thus retention of sodium and fluid initiates hypervolemia which ultimately causes hypertension (Ranpise et al., 2014). In spite of having best medical therapies to control blood glucose level, diabetic patients suffer from poorer cardiovascular outcomes than nondiabetic individuals. In majority of complex diseases like diabetes, multiple medications are essential to achieve the best therapeutic control as several mediators are involved in their pathogenesis (Siddiq and Khan, 2013). Likewise, the control of blood glucose level and management of other cardiovascular risk factors should be considered as very vital for diabetes care. The American Heart Association recommends that patients with diabetes should be treated as high risk cardiovascular patient and requires more rigorous blood pressure targets for the prevention of cardiovascular events. Hence, concurrent administration of antihypertensive medication is almost essential for proper management of diabetes in an appropriate antidiabetic

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drug regimen. With respect to the management of blood pressures in diabetic patients, it is very difficult to maintain a systolic blood pressure in patients with diabetes. For achieving this target, the patients need to be treated with either angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) (Trikudanathan and Graham, 2008).

It is well established that ARB class of antihypertensives is better tolerated than ACE inhibitors (Schmieder et al., 2011). Amongst ARBs, telmisartan has been reported with fewer drug-related adverse events and provides superior blood pressure control than ACE inhibitors (Schmieder et al., 2011).

Telmisartan was originally developed for the treatment of hypertension only. Modern available research evidence suggests that the ability of telmisartan to partially activate peroxisome proliferator-activated receptor (PPAR)-γ is useful particularly in treating hypertensive patients with diabetes mellitus. By activation of PPAR-γ, it improves insulin sensitivity in hypertensive patients with insulin resistance and has beneficial effect to decrease the glucose levels as well (Suksomboon et al., 2012). It would be thus better if an ARB is used for controlling hypertension in diabetes which has both glucose-lowering and blood pressure controlling potentials. Furthermore, ARBs exert renoprotective effects in addition to their blood pressure lowering effect, as they have direct defensive action on the diabetic kidney (Balakumar et al., 2012).

Pioglitazone, an oral antidiabetic agent in the class of thiazolidinediones, is widely used in type 2 diabetes as insulin sensitizers (Kaga et al., 2015; Temboonkiat et al., 2012). Pioglitazone has several distinct advantages over other oral antidiabetic agents. Pioglitazone increases the level of high density lipoprotein (HDL), decreases the level of triglycerides and most importantly decreases the events of cardiovascular diseases (Inzucchi et al., 2015). Hence, combination therapy of pioglitazone and telmisartan can provide a better therapeutic regimen for controlling the blood glucose levels and other associated cardiovascular complications in diabetic hypertensive patients. The beneficial effects of modulation of PPAR activity by combined administration of pioglitazone with telmisartan in treating multi-component metabolic syndrome are well documented (Haque, 2012).

But, the safety profile of established safe drugs may even get altered when they are administered as a combination of two or more. Complex drug interactions may result in an alteration of the toxicity profile of each ingredient rendering some drugs potentially toxic (Rao and Goldfrank, 1998). These potential drug interactions in terms of toxicological perspective should be studied well and documented properly before proceeding for their co-administration. In respect of pioglitazone and telmisartan, a number of toxicity studies have been carried out individually or in combination with other drugs of their own category (Berthet et al., 2011; Chinnam et al., 2012; Duan et al., 2009; Fouad et al., 2015; Gawly et al., 2009; Khudhair and Numan, 2014; Nandi et al., 2013; Sengupta et al., 2012; Weinberg et al., 2011). However there is no toxicity data available in support of possibility for co-administering these two particular drugs.

Thus, the aim of this study was to investigate the toxicity profile of the pioglitazone and telmisartan combination after simultaneous oral administration in rat to find out whether this combination is safe and free of any additional toxicity when they are co-administered.

2. Materials and methods

2.1. Chemicals

Telmisartan and pioglitazone were obtained from Hangzhou Hyper Chemicals Limited (Zhejiang, China). Formalin, ethanol, Xylene, hematoxylin and eosin were purchased from Fisher Scientific (M) Sdn. Bhd. Malaysia.

2.2. Animal husbandry and maintenance

Wistar albino rats (6 weeks age) of each sex (male and female) were used for this study. Rats were purchased from the commercial animal supplier We Love Pets, Petaling Jaya, Malaysia. The animals were grouped and housed in the wire cages with six animals per cage under controlled laboratory conditions. Animals were kept under good laboratory conditions (temperature 22 ± 2 °C; 48± 8% relative humidity) and were subjected to dark and light cycle (12 h/12 h) for 10 days before commencing the experiment to adjust them with the new environment and to overcome stress possibly incurred during transit. During this maintenance period, they had free access to standard dry pellet diet (Hartz, USA) and water ad libitum (La Boost Health Beverages Mfg Sdn Bhd, Malaysia). Only healthy and non pregnant animals were assigned for the study. The study was approved by the Institutional Animal Ethics Committee of Lincoln University College, Malaysia.

2.3. Toxicity study

2.3.1. Experimental design

The healthy male and female Wistar albino rats having weight between 178 and 195 g were divided into three treatment groups corresponding to pioglitazone (PIO), telmisartan (TLM) and mixture fraction (50:50 on weight basis) of pioglitazone-telmisartan combination (PTC) treatment and one control group. Each treatment group was subdivided into high, intermediate and low dose groups. Each subgroup consists of 6 male and 6 female rats similar to the control group. The drug was administered orally at three dose levels of 50, 100 and 150 mg/kg body weight corresponds to low dose, intermediate dose and high dose, respectively. For the PTC group, the PIO and TLM were administered simultaneously combining the individual dose levels of each drug at 50, 100 and 150 mg/kg body weight. The control group was treated with normal saline. The test substances were administered daily orally in graduate doses to the experimental animals for a period of 28 days. The study was performed to evaluate some basic important toxicity parameters in reference to the Organization for Economic Cooperation and Development (OECD) guidelines (OECD/OCDE 407, 2008).

2.3.2. Clinical observation

All the animals were observed daily for clinical signs of toxicity after dosing. Additionally, the animals were observed thrice in a day (immediately prior to dosing, in the morning and in the afternoon) for morbidity and mortality.

2.3.3. Body weight trends

Body weights of each rat were measured at the initiation of the treatment and once a week throughout the treatment period.

2.3.4. Food and water consumption

Food and water consumption in a group of 12 rats in two cages (six rats in each cage) were measured at the starting of treatment and weekly throughout the treatment period. The amount of food and water were calculated before they were supplied to each cage and their remnants were measured the next day to calculate the differences, which were regarded as daily food and water consumption (g/rat/day).

2.3.5. Hematology

For hematological investigation, rat blood was collected through