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Influence of Secindazole on Oral Hypoglycemic Activity of Glibenclamide and Pioglitazone on Albino & Diabetic Rat

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ABSTRACT: The present study was planned to study the influence of Secnidazole pretreatment (1 week) on the anti-diabetic activity of oral anti-diabetic agents in albino & Streptozotocin induced diabetic rats. Secnidazole (9 mg/kg) & Sulfonylureas like Glibenclamide (90µg/kg) and Pioglitazone (540µg/kg) were administered and the time to onset of hypoglycemia, duration of the hypoglycemia & peak hypoglycemia were determined. Then Secnidazole (9 mg/kg) was administered for 1week and on the next day 1 hour after Secnidazole treatment, the hypoglycemic effect of Sulfonylureas were evaluated. The results showed that coadministration of Secnidazole with Pioglitazone and Glibenclamide had positive influence on the peak hypoglycemic effect and a significant enhancement in the duration of hypoglycemic action in both normal and diabetic rats. This increased hypoglycemic activity of Pioglitazone and Glibenclamide after Secnidazole treatment may be due to improved insulin sensitivity and other insulin-resistant state in diabetes

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Keywords Secindazole; Diabetes; Metabolic Disorders.

INTRODUCTION

Diabetes is a disease, which requires treatment for lifetime. Further the diabetics are prone to be attacked by various infectious and other diseases. During such period it is essential to treat the co-existing diseases with more than one drug for a specified period. Keeping this in view, one can suspect that, a diabetic patient whose blood glucose has been stabilized by glibenclamide (GLB) or pioglitazone or combination of both may receive either ornidazole or secnidazole for protozoal, anaerobic or any other infection for specified period. However, there are reports that, when two or more drugs are administered concomitantly to a subject, there is every possibility that, one drug may influence the pharmacokinetic or pharmacodynamic profile of the other, leading drug-drug interactions [1]. Further, drug interaction has been reported to be the fourth to sixth leading cause of death in hospitalized patients [2]. These perplexing reports warrant the immediate necessity of studies to evaluate the possibility of life threatening drug-drug interactions among the probable multidrug prescriptions in clinical practice. Indeed, quite a big number of co-administered drugs with glibenclamide have been reported to either reduce or potentiate its hypoglycemic effect, leading to either reduced therapeutic efficacy or severe hypoglycemia and in certain cases death.

MATERIALS AND METHODS

Experimental animals- Albino rats of either sex weighing between 150-250 gm were selected for the study. Drugs- Secnidazole (Nicholas Piramal, Aurangabad.) Glibenclamide: (Cadila Health Care Ltd. Ahmedabad. Pioglitazone (Biocon Limited, Bangalore.); Streptozotocin (Sd- Fine-chemicals pvt. Ltd., Mumbai, India) Glucose Estimation Kit (Auto Span Liquid Gold, Span Diagnostics Ltd., Surat, India) and Autoanalyzer (Erba Mannheim chem-5 plus V2) were used in the present study. All the drugs used in this study were administered by suspending separately in 2% w/v gum acacia suspension in distilled water.

Induction of diabetes- The 2 groups of 6 albino rats were administered with 65mg/kg of streptozotocin dissolved in citrate buffer (0.1 M, pH 4.5) i.p. After 24 hours, blood samples were collected for determination of fasting glucose concentration. The rats with blood glucose level above 350 mg/dL were considered to be diabetic and were used in the experiment.

Sample Collection- The blood samples were collected by tail vein method 17, 18 at a time intervals (0, 0.5, 1, 2, 4, 8, 12, 18 and 24 hours) and centrifuged for 10 minutes at 5000 rpm, decanting supernatant fluid into the clean, dry test tube. Blood glucose level was estimated with the help of GOD/POD method using Erba Mannheim chem -5 plus V2 autoanalyser.

Evaluation of hypoglycemic action

(i**) Influence of Secnidazole on blood glucose levels in normal albino rats-** Suspension of Secnidazole (9 mg/kg) in 2%w/v of gum acacia was administered orally at the morning to all the rats (n=6) for one week. On the 7th day, 6 hours after administration of Secnidazole (9 mg/kg), the rats were fasted for 18 hours. On the 8th day, the blood samples were collected after the administration of Secnidazole (9 mg/kg) at different time intervals up to 24 hours.

(ii) **Effect of Secnidazole pre-treatment on the hypoglycemic activity of Pioglitazone and Glibenclamide in normal albino rats**- In the first part, the healthy rats of either sex (n=6) were divided into 2 groups. One received suspension of Pioglitazone (540µg/kg) in 2%w/v of gum acacia and other received Glibenclamide suspension (90µg/kg) through oral route and blood samples were collected at different time intervals (0, 0.5, 1, 2, 4, 8, 12, 18 and 24 hours). In the next part of this experiment, all the healthy rats were treated with Secnidazole orally for one week. On the 7th day, 6 hours after administration of Secnidazole, the rats were fasted for 18 hours. On the 8th day blood samples were collected for determining fasting blood glucose levels and Secnidazole was administered orally to all the animals. After 60 minutes, Pioglitazone (540µg/kg) or Glibenclamide (90µg/kg) was administered to animals. Blood samples were collected thereafter at different time intervals (0, 0.5, 1, 2, 4, 8, 12, 18 and 24 hours).

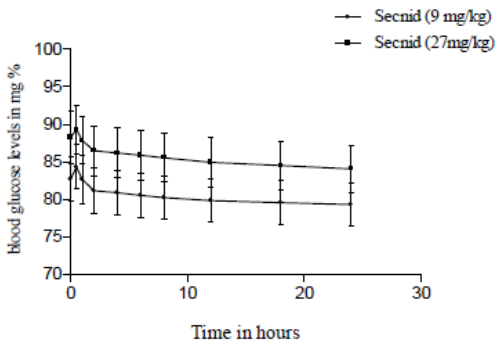
(iii) **Effect of Secnidazole pre-treatment on the antidiabetic activity of Pioglitazone and Glibenclamide in diabetic rats**- In the first part, the diabetic rats in a group (n=6) of 2 received suspension of Pioglitazone (540µg/kg) & Glibenclamide (90µg/kg) through oral route and blood samples were collected by tail vein.

In the next part, all the diabetic rats were treated with Secnidazole (9 mg/kg, p.o. once a day) for one week. On the 7th day, 6 hours after administration of Secnidazole, the rats were fasted for 18hours. On the 8th day, Secnidazole (9 mg/kg) was administered orally to all the animals. After 60 minutes, Pioglitazone (540µg/kg) & Glibenclamide (90µg/kg) were administered to animals. Blood samples were collected thereafter at 0.0, 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0 and 24.0 hours and analyzed for glucose levels by using GOD/POD method which was expressed as mg/100ml of blood. Then the hypoglycemic activity of Glibenclamide and Pioglitazone at time‘t’ was calculated and the % of blood glucose reduction at various time intervals were calculated before and after Secnidazole treatment.

RESULTS

Effect of secnidazole per se treatment on blood glucose levels in healthy albino rats- Treatment of Secnidazole (9 mg/kg) had positive influence on the blood glucose levels (32.37 ±1.40% reduction) in normal albino rats. The onset of action was observed between 1 to 2 hours and duration of action was 12 hours. This indicates that Secnidazole has a hypoglycemic effect in healthy rats. The results are graphically depicted in Fig. 1.

Fig.1- Effect of Secnidazole (9 mg/kg) per se treatment on blood glucose levels in normal albino rats.



Influence of Secnidazole pre-treatment on Pioglitazone and Glibenclamide induced hypoglycemia in healthy albino rats-

Secnidazole pre-treatment (9mg/kg p.o.) once a day for 7 consecutive days with Pioglitazone and Glibenclamide had not significantly altered the onset of hypoglycemia (1 hour before treatment and 1 hour after treatment). Pioglitazone significantly affected peak hypoglycemia (39.32 ± 1.08% before treatment and 46.46 ± 0.93% after treatment), however duration of hypoglycemia was observed 12 hrs before treatment and 18 hrs after treatment.

Glibenclamide enhanced the peak effect (41.44 ±0.54% reductions before treatment to 51.81 ±0.74 % reductions after treatment) and duration of hypoglycemia was also enhanced from 12 hrs to 24 hrs. The results of these findings are graphically depicted in Fig. 2, 3.

Fig. 2- Influence of Secnidazole (9 mg/kg) on hypoglycemia induced by Pioglitazone in healthy albino rats.

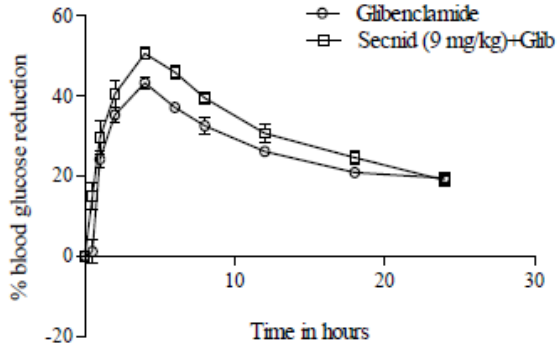
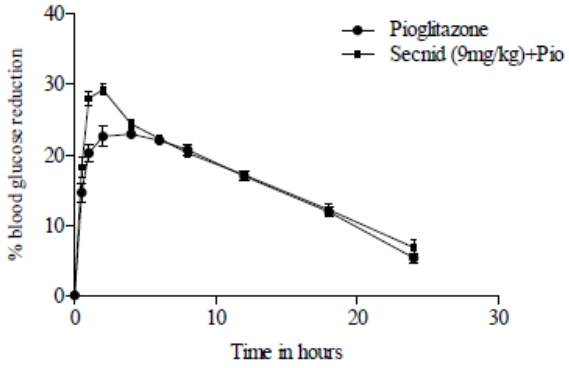


Fig. 3- Influence of Secnidazole (9 mg/kg) on hypoglycemia induced by Glibenclamide in normal albino rats



Influence of Secnidazole pre-treatment on the Pioglitazone and Glibenclamide induced hypoglycemia on diabetic albino rats

In diabetic rats, pre-treatment of Secnidazole (9 mg/kg) once a day for 7 consecutive days, with Pioglitazone and Glibenclamide significantly decreased onset of hypoglycemic action (from 1 hour before treatment to 0.5 hour after treatment). Pioglitazone increased peak hypoglycemia (35.19± 0.44% reduction before treatment to 44.21± 0.29% after treatment) and duration of hypoglycemia was enhanced from 12 to 24 hours Also Glibenclamide increased peak hypoglycemia (41.65± 0.38% before treatment and 50.14± 0.41% after treatment) and duration of hypoglycemia was increased from 12 to 24 hours. The results of these findings graphically depicted in Fig. 4, 5.

Fig. 4- Influence of Secnidazole (9 mg/kg) on hypoglycemia induced by Gilbenclamide in diabetic rats

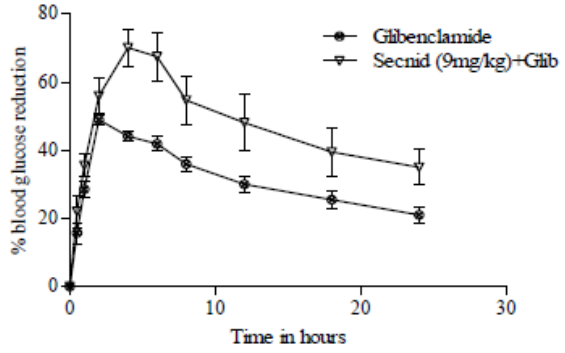
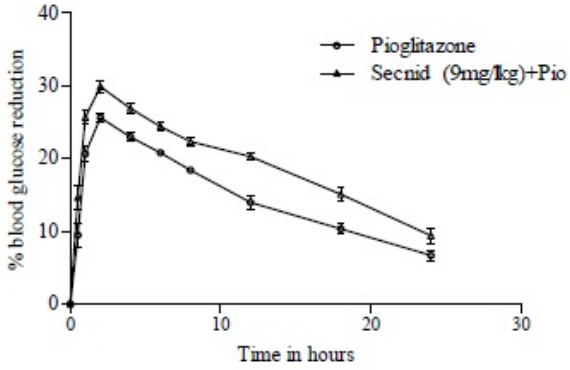


Fig. 5- Influence of Secnidazole (9 mg/kg) on hypoglycemia induced by Pioglitazone in diabetic rats



DISCUSSION

Infectious diseases and DM are two common chronic conditions which frequently coexist and can significantly affect individual health care needs. Secnidazole is structurally related to the commonly used 5-nitroimidazoles metronidazole and tinidazole. These drugs share a common spectrum of activity against anaerobic micro-organisms and they appear particularly effective in the treatment of amoebiasis, giardiasis, trichomoniasis and bacterial vaginosis [3]. Reports witness that, 5-nitroimidazoles increase the dose related toxicities of several coadministered drugs which are substrates to either 2C9 or 3A4 or to both [4-9]. Similarly the study drugs ornidazole and secnidazole potentiate the anticoagulant activity of warfarin a2C9 substrate [10-13]. Hence, it would be possible that, if ornidazole or secnidazole is coadministered

with long term pioglitazone, there may be exaggeration of dose related toxicity of the latter. Pioglitazone can cause fluid retention and peripheral oedema, which can lead to or exacerbate heart failure and pulmonary oedema [14]. The precise mechanism of this adverse reaction is not known, but it appears to be a dose-related class effect of the thiazolidinediones [15].

However, in the present study no such adverse events have been noticed and there was statistically significant and may be clinically insignificant influence on the glucose lowering effect of pioglitazone and secnidazole. It is observed that, the blood glucose levels after coadministratio of secnidazole with pioglitazone was not indicating severe hypoglycaemia. Therefore it was inferred that, this elevation in hypoglycaemia due to coadministration of study drugs and pioglitazone is clinically insignificant. Hence at this juncture it is concluded that, coadministration pioglitazone with secnidazole is harmless at therapeutic doses, yet deliberate caution is required in clinical usage of this combination. Indeed, long term studies involving diabetic subjects would provide quite rewarding results. Since the pretreatment with therapeutic doses of study drugs did exihibit drug interactions to a lesser extent with pioglitazone, this study on these combinations was not furthered. Concurrent use of Secnidazole and anti-diabetic agents usually appears to produce hypoglycemia, but uneventful. Increased hypoglycemic and anti diabetic activity of Pioglitazone and Glibenclamide after Secnidazole treatment may be due to improved insulin sensitivity and other insulin-resistant state in diabetes as these are reported with Secnidazole. The results showed that pretreatment of Secnidazole in diabetic rats has shortened the onset of antidiabetic activity and enhanced the duration of action from 12 to 24 hours of Pioglitazone as well as Glibenclamide. Also it causes significant increase in peak hypoglycemic effect of Pioglitazone and Glibenclamide i.e. from 35.19 % to 44.21 % and from 41.65% to 50.14% respectively. From the results obtained, it can be indicated that repeated treatment of Secnidazole exerts a definite additive or synergistic pharmacodynamic effect on hypoglycemic/ antidiabetic action of Pioglitazone and Glibenclamide, not only in normal state but also in diabetes conditions. It was observed from result that Secnidazole appears primarily to give additive or synergistic pharmacodynamic effect with enhanced insulin sensitivity by utilization of glucose in skeletal muscles, increase in micro and macro vascular circulation to pancreas and decreased insulin resistance.

CONCLUSION

Secnidazole pre-treatment increases the hypoglycemic and anti-diabetic activity of Pioglitazone and Glibenclamide. The additive or synergistic pharmacodynamic drug-interaction between Secnidazole and antidiabetic drugs like Pioglitazone and Glibenclamide must be considered during their long term treatment in diabetic patients and proper dose adjustment to avoid severe hypoglycemia.

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