Acta Pharmaceutica Sciencia
50: 137-143 (2008)

Influence of Secnidazole on Glibenclamide-Induced Hypoglycaemia in Albino Rats

J. Bheemachari [1], S. Ramachandra Setty [2*], M. Lakshmi Narasu [3]

[1] Department of Pharmacology, N. E. T. Pharmacy College, Raichur.
[2] Department of Pharmacology, S. C. S. College of Pharmacy, Harapanahalli.
3 Department of Biotechnology, J .N. T. University, Hyderabad, India.

Abstract

Secnidazole is structurally related to the commonly used 5-nitroimidazoles metronidazole and tinidazole. They are active against anaerobic micro-organisms and are particularly effective in the treatment of amoebiasis, giardiasis, trichomoniasis and bacterial vaginosis. The highest cure rate combined with a good tolerability profile, make secnidazole a suitable option to other drugs in this class. However 5-nitroimidazoles have been reported to interact with a number of concomitantly used drugs and potentate their therapeutic action; secnidazole is no exception. Nevertheless, its interaction with glibenclamide a frequently used sulfonylurea has not yet been properly studied and reported. Hence, in the present pre-clinical study the influence of secnidazole on the glibenclamide-induced hypoglycaemia in albino rats was considered. Secnidazole (9mg/kg, p.o; BD, for 7 days) and (27 mg/kg, p.o; BD, for 3days) pre-treatment was found to potentate the glucose lowering effect of glibenclamide (90µg/kg p.o) significantly. Hence, it was concluded that, restructuring of glibenclamide dose and/or frequency of its administration is necessary when used concomitantly with secnidazole, to keep tight glycemic control.

Key Words: albino rats, enzyme inhibition, glibenclamide, interaction, secnidazole

Introduction

Secnidazole is structurally related to the commonly used 5-nitroimidazoles metronidazole and tinidazole. They are active against anaerobic micro-organisms and are particularly effective in the treatment of amoebiasis, giardiasis, trichomoniasis and bacterial vaginosis. It is rapidly and completely absorbed after oral administration and has a longer terminal elimination half-life (approximately 17 to 29 hours) than commonly used drugs of this class. The documented report reveals that, in patients with intestinal amoebiasis or giardiasis, clinical or parasistological cure rates of 80 to 100% are achieved after treatment with a single dose of secnidazole 2g (30 mg/kg in children), similar to the response rates achieved with multiple dosage regimens of metronidazole or tinidazole. Patients with hepatic amoebiasis appear to respond well to 5 to 7 day therapy with secnidazole. After administration of a single dose of secnidazole, parasitological eradication was achieved in approximately 92 to 100% of patients with urogenital trichomoniasis. In the clinical trials reviewed, secnidazole was well tolerated; adverse events did not require treatment intervention or withdrawal from therapy. The highest

* Corresponding author: rssiddamsetty@yahoo.co.in

cure rate combined with a good tolerability profile, make secnidazole a suitable option to other drugs in this class (Gillis and Wiseman, 1996). However 5-nitroimidazoles have been reported to interact with a number of concomitantly used drugs and potentate their therapeutic action; secnidazole is no exception (Hansten, 1985; Tatro and Olin, 1985; O'Reilly, 1976; Kazmier, 1976; Dean and Talbert, 1980; Teicher *et. al.,* 1987). Nevertheless, its interaction with the glibenclamide, a widely used antidiabetic agent has not yet been properly studied and reported. Hence in the present pre-clinical project, an effort has been made to study and understand the influence of secnidazole on glibenclamide induced hypoglycemia in albino rats.

Materials and Methods

Drugs and chemicals: Secnidazole (Nicholas Piramal Limited, Mumbai), Glibenclamide (Cadila Health Care Ltd, Ahmedabad) and the glucose estimation kit of Autospan Diagnostics Ltd, Mumbai, were used in the study.

The study protocol was duly approved by the Institutional Animal Ethics Committee and was conducted in accordance with the NIH guidelines, in an institution, approved by the CPCSEA.

The drugs secnidazole and glibenclamide are used orally in the clinical practice; hence, the same route was followed. Further, secnidazole is prescribed either a single stat dose or 5 to 7 days regimen in clinical practice, depending on the organism involved and severity of infection. Hence in the present study, a single dose and seven days pre-treatment was considered to be most appropriate to simulate the clinical situation and was adopted. The doses of secnidazole and glibenclamide were calculated by extrapolating the human dose to rat dose (Laurence and Bacharach, 1964).

As secnidazole and glibenclamide are sparingly soluble in water, they were suspended separately in 2% w/v acacia suspension in triple glass distilled water for oral administration. Plain acacia suspension (2% w/v) was used as a vehicle.

Experimental: Albino rats of either sex weighing between 167-218 grams were randomly distributed into five groups each consisting of 6 animals. They were housed in clean polypropylene cages and fed with commercial pelleted rat chow diet and water was given *ad libitum.*

Animals of all the groups were fasted for 18 hours before experimentation and fasting was continued till the end of experimentation. However, water was allowed freely throughout the period of experimentation.

Experiment on groups I, II, III and IV were carried out in single phase. Where as for the group V it was conducted in two phases.

The animals of group-I and II were administered with acacia suspension (2% w/v) (volume matched with the average volume of secnidazole dose) and secnidazole suspension 9 mg/kg, p.o; twice daily, for seven consecutive days, respectively. On seventh day, six hours after respective treatment (acacia suspension/secnidazole) food was deprived and water was allowed *ad libitum.* On 8^{th} day, one hour after respective treatment (acacia suspension/secnidazole), one more dose of the same was repeated. There after blood samples (0.5 ml) were collected from the tail vein at intervals of 0, 0.5, 1, 2, 4, 6, 8, 12, 18 and 24^{th} hours and analyzed for blood glucose concentration (Trinder, 1969).

Group III and IV received secnidazole (27 mg/kg, p.o, O.D). On the same day, exactly after one hour, group III was administered with one more dose of secnidazole, where as group IV received glibenclamide (90 µg/kg, p.o). Thereafter blood samples were collected from the tail vein at above specified time intervals and analysed for the glucose concentration (Trinder, 1969).

The experiments on the group V was conducted in two phases as follows.

Phase-I: all the animals of group V were administered with glibenclamide (90 µg/kg, p.o) and thereafter blood samples were collected from the tail vein at above specified time intervals and analysed for the glucose concentration (Trinder, 1969).

Phase-II: after one week of wash out period, the animals of group V were administered with secnidazole 9 mg/kg, p.o; twice daily for seven consecutive days. On seventh day six hours after secnidazole administration food was deprived and water was allowed *ad libitum.* On 8th day one hour after secnidazole administration, glibenclamide (90 µg/kg, p.o) was administered. The blood samples (0.5 ml) were collected from the tail vein at above specified time intervals and analyzed for blood glucose concentration (Trinder, 1969).

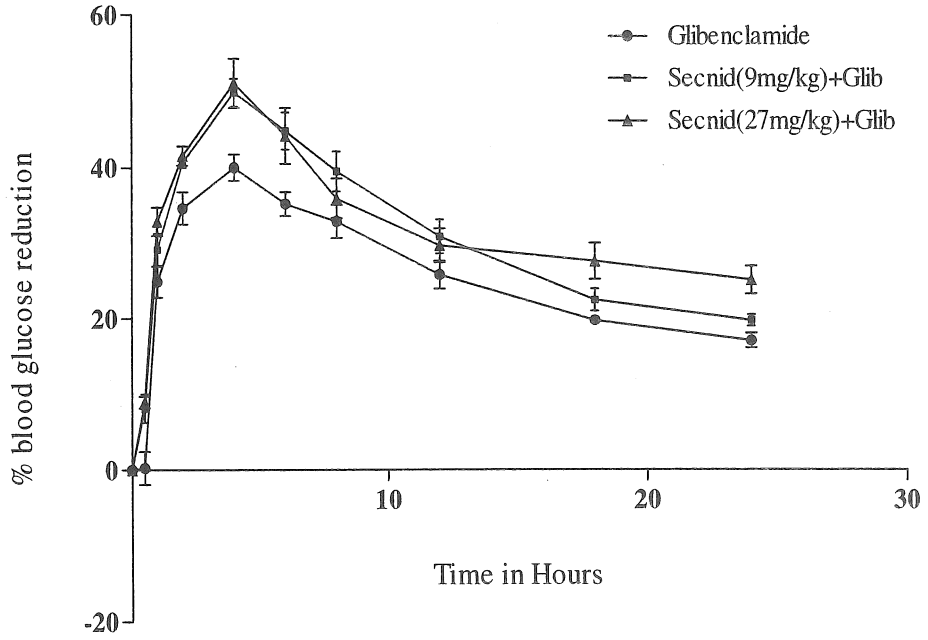
The hypoglycaemic effect due to particular treatment at any required point of time 't'(if any) was calculated as the percentage blood glucose reduction at that time with respect to basal blood glucose level.

Statistical analysis: The data is presented as mean ± SEM and was anlysed by using One Way Analysis of Variance (ANOVA) followed by Dunnett's multiple comparison tests. p values lower than 0.05 were considered statistically significant.

Results and discussion

The results of study are compiled in Tables 1and 2, and graphically depicted in Figure 1.

Figure 1. Influence of secnidazole on glibenclamide induced hypoglycemia in rats



For the assessment of hypoglycemia, onset of action (time taken for 20% reduction in blood glucose level), peak effect and duration of hypoglycemia (duration during which at least 20% reduction in blood glucose levels were maintained) were considered.

From Table 2, it is quite apparent that, acacia suspension (2% w/v) which is used as vehicle for administration of the drugs, by itself is devoid of any hypoglycemic activity. Hence, hypoglycemic effect observed due to any particular drug treatment using acacia suspension as

vehicle is solely due to drug administered and not because of vehicle. Further the data also rules out the significant contribution of long term starvation (42 hours) on hypoglycemic activity due to any particular drug treatment. It is quite evident from the Table 2 that, secnidazole (9 mg/kg, p.o; twice daily for seven consecutive days and 27 mg/kg, p.o; OD respectively) treatment *per se* has no significant influence on the blood sugar levels in rats.

From Table 2 it is quite obvious that, the onset of action of glibenclamide was within one hour; the peak hypoglycemic effect was observed at 4^{th} hour (41.47±1.61%) and duration of action was maintained between 12-18 hours.

The secnidazole (9 mg/kg, p.o; twice daily for seven consecutive days and 27 mg/kg, p.o; OD respectively) pretreatment produced very significant alteration in glibenclamide induced hypoglycemia. The peak effect was significantly increased from 40.05±1.73 % to 49.83±1.82 % ($p < 0.05$) and 51.06±3.25 % ($p< 0.01$) respectively (Table 2) at 4^{th} hour and there was prolongation of hypoglycemic action from 18 hours to more than 24 hours. However, there was no change in onset of hypoglycemic action, which is within half an hour both before and after the secnidazole treatment. In both the groups, out of six animals studied, three animals exhibited complete lack of physical activity (symptom of severe hypoglycemia) and other three exhibited severe hypoglycemic convulsions and recovered.

For successful combating clinical challenges, several new drugs are approved and introduced every year with improved profile over the existing ones. However, the influence of these agents on the frequently used drugs with low or narrow therapeutic index needs to be continuously evaluated and reported to avoid the unexpected hazards. Since several drugs have been reported to strongly influence the hypoglycemic action of glibenclamide, leading to a clinical emergency (Furuta, et. al., 2001; Lee et. al., 1987; Ko et. al., 1997; Rambhimaiah et. al., 2003; Bheemachari and Setty, 2005). In the present study, two frequently used doses of secnidazole were evaluated for their influence on the glibenclamide induced hypoglycemia. It is quite evident from the results that (Tables 1 and 2), concomitant use of secnidazole (both doses) exaggerated the hypoglycemic effect of glibenclamide at 4^{th} hour (Tables 1 and 2) and led to total lack of physical activity in half of the test population and hypoglycemic convulsions in the rest. Reported data indicate that, several concomitantly used drugs potentate the hypoglycemic effect of glibenclamide by inhibition of microsomal enzymes responsible for its metabolism (Furuta et. al., 2001; Lee et. al., 1987; Ko et. al., 1997; Rambhimaiah et. al., 2003; Bheemachari and Setty, 2005). In analogy with the same, at this juncture, it can be attributed that, the exaggerated hypoglycemic effect of glibenclamide in the present study may be due to enzyme inhibition by the secnidazole. However evaluation of the same conducting pharmacokinetic studies will be quite rewarding.

In conclusion, co-administration of secnidazole and glibenclamide may give rise to therapeutic problem leading to severe hypoglycemia. This is particularly important in elderly subjects, since, hypoglycemia can present as an acute neurological emergency that may mimic cerebrovascular accident. So, the dose and / frequency of sulfonylurea administration should be readjusted accordingly, when they need to be co-administered with secnidazole to avoid fatal hypoglycemia.

Table 1. Blood glucose levels (mg %) at different time intervals (following various treatments in healthy albino rats)

Time in Hrs	blood glucose levels (mg %), Mean ± SEM					
	Acacia suspension	Secnidazole (9mg/kg, p.o, BD, 7 days)	Secnidazole (27 mg/kg, p.o, OD)	Glibenclamide (90 µg/kg, p.o)	Secnidazole (9 mg/kg, p.o, BD, 7 days) + Glibenclamide (90 µg/kg, p.o)	Secnidazole (27 mg/kg, p.o, OD) + Glibenclamide (90 µg/kg, p.o)
Fasting	80.10 ± 3.07	82.68±2.97	88.25±3.45	90.80±2.19	90.34±1.43	88.36±2.77
0.5	80.87 ± 2.87	84.32±2.93	89.32±3.28	90.51±2.59	82.97±2.34	80.42±2.72
1.0	80.88 ± 2.64	82.67±3.19	87.85±3.14	68.20±2.57	64.10±2.66	59.37±2.66
2.0	78.81 ± 1.83	81.16±2.98	86.49±3.29	59.44±2.73	53.66±1.41	51.69±2.16
4.0	76.36 ± 3.17	80.88±2.97	86.18±3.32	54.39±1.85	45.42±2.22	43.47±3.79
6.0	77.42 ± 3.70	80.53±2.92	85.88±3.27	58.74±1.39	49.79±2.17	49.13±3.10
8.0	76.67 ± 3.85	80.23±2.91	85.54±3.20	60.79±1.60	54.55±2.17	56.48±2.60
12.0	76.43 ± 3.63	79.83±2.88	84.94±3.24	67.32±2.19	62.46±1.26	62.06±2.57
18.0	76.79 ± 3.11	79.56±2.92	84.50±3.19	72.81±1.73	69.98±1.30	63.80±2.20
24.0	77.10 ± 3.25	79.30±2.88	84.06±3.14	75.25±1.75	72.44±1.04	66.03±2.09

Table 2. Percentage decrease in blood glucose levels at different time intervals (Following various treatments in healthy albino rats)

Time in Hrs	% reduction in blood glucose concentration, Mean ± SEM					
	Acacia suspension	Secnidazole (9mg/kg, p.o, BD, 7 days)	Secnidazole (27 mg/kg, p.o, OD)	Glibenclamide (90 µg/kg, p.o)	Secnidazole (9 mg/kg, p.o, BD, 7 days) + Glibenclamide (90 µg/kg, p.o)	Secnidazole (27 mg/kg, p.o, OD) + Glibenclamide (90 µg/kg, p.o)
Fasting	---	---	---	---	---	---
0.5	-1.03 ± 0.74	-2.00±0.17	-1.27±0.56	0.25±2.19	8.19±1.88 [a]	9.01±0.79 [b]
1.0	-1.12 ± 1.37	0.04±0.88	0.37±0.67	24.90±2.06	29.14±2.13 [ns]	32.86±1.88 [a]
2.0	1.21 ± 2.67	1.85±0.15	1.97±0.19	34.61±2.15	40.65±0.67 [b]	41.56±1.25 [c]
4.0	4.54 ± 2.51	2.19±0.19	2.33±0.13	40.05±1.73	49.83±1.82 [a]	51.06±3.25 [b]
6.0	3.43 ± 1.95	2.61±0.05	2.66±0.15	35.20±1.61	44.85±2.42 [a]	44.17±3.63 [ns]
8.0	4.44 ± 1.82	2.97±0.05	3.04v0.21	32.89±2.19	39.54±2.65 [ns]	35.95±2.64 [ns]
12.0	4.71 ± 1.41	3.45±0.06	3.73±0.12	25.82±1.85	30.87±2.26 [ns]	29.69±2.26 [ns]
18.0	4.15 ± 0.79	3.79±0.10	4.22±0.16	19.79±0.64	22.48±1.47 [ns]	27.61±2.39 [b]
24.0	3.79 ± 0.93	4.09±0.06	4.71±0.20	17.09±0.98	19.79±0.76 [ns]	25.14±1.86 [c]

values are mean ± SEM, (n=6); statistically significant as follows, compared with glibenclamide treated group.
'a' represents $p < 0.05$
'b' represents $p < 0.01$
'c' represents $p < 0.001$
'ns' represents non-significant

Acknowledgements

The authors express their deep gratitude to M/s. Panacea biotec Ltd, New Delhi and M/s. Cadila Health Care Ltd, Ahmedabad for sparing gift samples of secnidazole and glibenclamide respectively. One of the authors Mr. Bheemachari, expresses sincere thanks to Dr. R. H.Udupi, Professor & Head, N.E.T.Pharmacy College, Raichur, for critical evaluation of the paper and to Dr. S. Ramabhimaiah, Professor & Head and Dr. Misri Khan Khaleel, Professor, Department of Pharmacology, Navodaya Medical College, Raichur, for their valuable suggestions and discussions.

References

Anticoagulants, oral/metronidazole. In: Tatro, D.S., Olin, B.R., eds. (1988). Drug interaction facts, St. Louis: JB Lippincott Co, p 82.

Bheemachari, J., Ramachandra Setty, S. (July 2005). Influence of Higher Dose of Itraconazole on Sulfonylurea-Induced Hypoglycemia in Albino Rats. *The Antiseptic.* Vol. 102 No. 7: 376-378.

Dean, R.P., Talbert, R.L. (1980). Bleeding associated with concurrent warfarin and metronidazole therapy. *Drug Intell. Clin. Pharm.* 14: 864-6.

Furuta, S., Kamada, E., Suzuki, T., Sugimoto, T., Kawabata, Y., Shinozaki, Y., Sano, H. (2001 Jan). Inhibition of drug metabolism in human liver microdomes by nizatidine, cimetidine and omeprazole. *Xenobiotica* 31(1): 1-10.

Gillis, J.C., Wiseman, L.R. (1996 Apr). Secnidazole. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. *Drugs* 51(4): 621-38.

Hansten, P.D. (1985). Drug interactions 5th ed. Philadelphia: Lea & Febiger; 96.

Kazmier, F.J. (1976). A significant interaction between metronidazole and warfarin. *Mayo Clin. Proc.* 51: 782.

Ko., Jae-wook., sukhova., Nadia., Thacker., David., Chen., Patricia., Floockhart and David, A. (1997). Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. *Drug. Metab. Dispos.* 25(7): 853-62.

Laurence, D.R., Bacharach, A.L. (1964). Evaluation of drug activities and Pharmacometrics. Academic Press London and New York.1: pp. 160-161.

Lee, K., Mize, R and Lowenstein, S.R. (1987). Glyburide-induced hypoglycemia and ranitidine. *Ann. Intern. Med.* 107: 261-2.

O'Reilly, R.A. (1976). The stereoselective interaction of warfarin and metronidazole in man. *N. Engl. J. Med.* 295: 354.

Rambhimaiah, S., Suresh, D.K., Gupta, V.R.M., Bheemachari., Ravi Prakash, P. and Srinivas Rao, P. (Sept. 2003). Influence of Metronidazole on the hypoglycemic effect of Tolbutamide in Healthy Albino Rabbits. *Indian Drugs* 40(9): 535-38.

Teicher, M.H., Altesman, R.I., Cole, J.O. (1987). Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 257: 3365-6.

Trinder, P. (1969). Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor. *Ann. Clin. Biochem.* 6: 24-7.

Received: 4.01.2008
Accepted: 12.02.2008