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DETERMINE THE PHARMACOKINETIC PARAMETERS IN WISTAR ALBINO RATS

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Abstract

The medication gliclazide is often used for patients with type 2 diabetes. Studies looking back in time have shown that diabetics are more likely to have serious consequences after an amoebic infection. One of the most used antiamoebic drugs is ornidazole. The purpose of this research was to assess the efficacy and safety of a combination of gliclazide and ornidazole in the treatment of type 2 diabetes in normal rats by monitoring changes in blood sugar levels and observing the drug's activity and pharmacokinetics. Two milligrams of gliclazide per kilogram of body weight and twenty-five milligrams of ornidazole per kilogram of body weight were given orally to normal rats in studies. At predetermined intervals, blood was drawn from the orbital sinuses of the rats. Based on the findings of the current investigation, it seems that ornidazole lacks glucose-lowering efficacy and that any drug-drug interactions between ornidazole and gliclazide are likely of the pharmacokinetic type, with the putative interaction being related to CYP2C9 suppression. It follows that caution is warranted when prescribing ornidazole and gliclazide together for their therapeutic benefit in diabetic patients, and that the dosages may need to be slightly adjusted. But there should be more research done.

Key words: Albino wistar rats, Cytochrome P 2C9, Gliclazide, HPLC Ornidazole, Pharmacokinetic interactions.

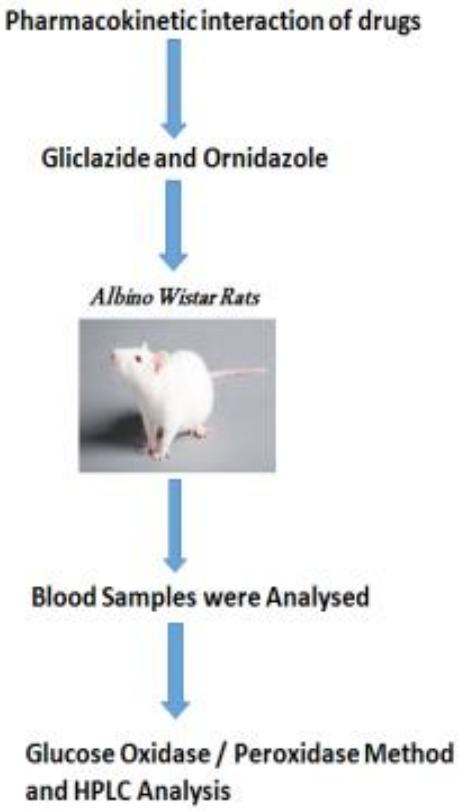
INTRODUCTION

Elevated blood glucose levels and disruptions in carbohydrate, lipid, and protein metabolisms characterize diabetes mellitus, a chronic metabolic disorder linked with several health problems across multiple organ systems. More than quadrupling is expected by the year 2030, from the current prevalence of 143 million cases worldwide. Type 1 and type 2 diabetes are caused by the pancreas's -cells not producing or secreting enough insulin. Because of its selective inhibitory activity towards pancreatic K+ATP channels, anti-oxidant property, low incidence of producing severe hypoglycemia, and other haemo-biological effects, the second-generation sulfonylurea derivative gliclazide is the drug of choice for the treatment of type-2 diabetes. Blocking K+ ATP channels allows calcium to enter pancreatic cells, where it stimulates insulin secretion. Previous research has shown that gliclazide, like many other anti-diabetic treatments, interacts with a wide variety of other medications.

The potential for adverse medication reactions grows as the patient's therapy regimen becomes more complex. Studies of drug interactions are particularly crucial for medications with a low safety margin and for long-term usage of any medication. Protozoal infections, such as the amoebiasis that resulted in an amoeboma, are very unusual but have been reported in a number of diabetic individuals. The symptoms matched those of a bowel obstruction caused by a tumor, which is amenable to pharmaceutical intervention.

The primary objective of pharmacological therapy for IBD relapses is to decrease the inflammatory process. The analgesic, antipyretic, and anti-inflammatory properties of 5-aminosalicylates set them out as a class of non-steroidal anti-inflammatory medicines (NSAIDS). While these substances have a local

impact on the mucosa of the colon, they may cause systemic symptoms such weakness, hepatic abnormalities, arthralgia, and myalgia in addition to the more common ones like diarrhea, nausea, vomiting, headache, and abdominal discomfort. The sulfapyridine in mesalazine is thought to be responsible for the drug's negative effects.



LITERATURE REVIEW

V Rama Krishna, et al. (2011), The goal of this research was to examine the effects of single and repeated doses of glibenclamide on the pharmacokinetics and pharmacodynamics of eprosartan, a prototype medication used to treat diabetic nephropathy, in healthy Albino Wistar rats. Glibenclamide and eprosartan were administered to the animals at therapeutic doses (TD). Pharmacokinetic parameters were calculated using an estimation of blood glucose levels using the GOD/POD technique and an estimation of plasma glibenclamide concentrations using a sensitive RP HPLC method. Eprosartan inhibits P-glycoprotein mediated transport of glibenclamide, which may explain why eprosartan- and glibenclamide-treated rats showed a greater percentage reduction in blood glucose levels and glibenclamide concentrations than glibenclamide-treated rats did in a single-dose study. The current investigation confirmed that eprosartan and glibenclamide had a pharmacokinetic and pharmacodynamic interaction. There is a chance that P-gp and CYP enzymes will work together. Drug-drug interactions may be avoided in clinical settings if their occurrence is first studied in pre-clinical settings.

AlRasheed, H.; et al. (2019). When ASP 1000 mg/kg was administered, there was a 159% increase in ERL Cmax and a 73% decrease in GEF Cmax. ASP 1000 raised ERL's AUC0-72 but lowered GEF's AUC0-. ERL had a 64% drop in CL/F while GEF saw a 38% rise. In addition, the findings showed that after two weeks of dosing, ASP dramatically elevated levels of liver enzymes. Conclusions: Both ASP 175 and 1000 mg/kg change ERL and GEF PKs characteristics, however the effect of the higher dose is

more pronounced for most measures. There is some evidence that ASP at 1000 mg/kg might cause liver damage by dramatically elevating hepatic enzyme activity. Thus, it may be clinically significant to avoid giving aspartame-containing items to patients receiving ERL or GEF treatment.

Gour, Dogra, Sharma, Wazir, and Nandi (2018). Maximum plasma concentrations, elimination half-lives, and area under the curve for bedaquiline were all considerably lower in streptozotocin-induced diabetic rats compared to their equivalent values in the normal group, whereas clearance was much higher. Clinical research is important to establish that an adjustment in bedaquiline dose is required in the diabetic mellitus state, which is vital to prevent therapeutic failure. Bedaquiline's pharmacokinetics in a preclinical animal with renal impairment and diabetes mellitus have never before been reported.

Mohammed Gayasuddin Mouid, (2015), An adverse drug reaction occurs when a drug is combined with another substance that alters the medication's intended effects. Herbal CAM is often used alongside conventional treatment, however patients don't always tell their doctors about their herb usage, which might increase their risk of adverse drug reactions. Due to the similarity between the metabolic processes involving CYP2C9 and CYP3A4 enzymes, the current research seeks to determine whether or not the herbal medicine. To reduce the risk of Gliclazide's side effects, it's possible to utilize supplemental formulations that include Andrographis paniculata, although doing so requires careful monitoring and maybe dosage adjustments.

J. Yuan; et al. (2017), The current investigation aimed to compare the pharmacokinetics of diclofenac sodium (DIC) after a single intravenous (i.v.) and oral (p.o.) dose in Sprague-Dawley (SD) rats. There were a total of 12 male SD rats used, 6 in one group that received an intravenous injection of 2 mg/kg DIC and 6 in the other group that received a lavage with the same dose. Blood samples were taken before (0 h), during (0.033 h), and after (0.167 h), 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, and 8 h of DIC administration. After treating blood plasma samples to precipitate proteins, they were examined using liquid chromatography-mass spectrometry (LC-MS/MS). Important pharmacokinetic parameters were calculated using pharmacokinetics software that implemented the non-compartmental model. Clearance (CL), apparent volume of distribution (Vz), mean residence time (MRT), and steady-state apparent volume of distribution (Vss) are all measures of how quickly a drug leaves the body after it has reached its terminal concentration for DIC after intravenous administration were 0.570.05 l/h, 1.220.11 h, 3356238 h ng/ Calculated values for z, t12, Cmax, tmax, AUC0-, CL, Vz, and MRT after oral DIC treatment are as follows: 0.630.12 l/h; 1.120.18 h; 1272112 ng/ml; 0.190.04 h; 2501303 h ng/ml; 0.810.10 l/h; 1.290.12 l; and 2. Fast absorption, distribution, and elimination are all shown by the pharmacokinetic characteristics of i.v. and p.o. DIC in rats.

MATERIALS AND METHODS

Dr. Reddy's Laboratories supplied the gliclazide, while Sri SJS Pharma supplied the ornidazole. Excel Diagnostics' glucose testing kits are sourced domestically. J.T. Baker was the source for the HPLC grade acetonitrile and methanol used in this experiment. In addition, only analytical-grade compounds were utilized.

Albino rats, both male and female, were employed for the experiment. The Mahaveer Enterprises animals were housed for a week at a minimum in a room maintained at 25 2oC, 50% relative humidity, and a 12 hour light/12 hour dark cycle. Institutional Animal Ethics Committee clearance was obtained before any animal studies were conducted at the Vaagdevi College Labs.

Investigation of Drug Interactions in Healthy Albino Wistar Rats

Suspensions of gliclazide and ornidazole were made with gum acacia at a concentration of 2% w/v. Oral gavage was used to provide both medications to their designated groups. After 1, 2, 3, 4, 6, 8, 12, and 24 hours of therapy, blood samples were collected from the orbital sinuses of the animals via retro puncture into centrifugation tubes containing 0.1 mL 0.2% sodium citrate while the animals were under diethyl ether anesthesia. The plasma was centrifuged off and then frozen at -20 degrees Celsius for later use. Both glucose estimation and HPLC analysis rely on these specimens. The glucose oxidase/peroxidasekit was used to estimate blood sugar levels.

Bioanalytical method

Measurements of gliclazide concentrations in plasma were made using a Waters 2487 HPLC system equipped with a Kromasil 100-5C18 column, an SPD-20A UV detector, a solvent delivery module LC-20AD, and an operating wavelength of 230 nm.

Before adding the spikes, all the samples were mixed by being vortexed for 10 seconds. Fifty liters (L) of the working solution containing the internal standard were added to a serum aliquot (100 L). One milliliter of methanol was added to this. A 50 L aliquot of the reconstituted dry extract was introduced into the HPLC apparatus after being reconstituted with 100 L of the methanol. The elution times for gliclazide and the IS were 5.8± 1.1 and 8.6± 1.1 minutes, respectively. The data were presented as a mean SD. Unpaired t test was used to find the significance.

RESULTS

This investigation disproved the hypothesis that ornidazole might reduce blood sugar levels. When gliclazide is given alone or in conjunction with ornidazole, there are no discernible changes in plasma blood glucose levels (Table 1). Figure 1 depicts the time course of blood glucose reduction for gliclazide, ornidazole, and the combination of gliclazide and ornidazole. As can be seen in (Figure 2), coadministration of ornidazole with several doses of gliclazide considerably affected the pharmacokinetic parameters of gliclazide.

Table 1: Reduction of blood glucose levels

Time interval (hr)	Ornidazole	Gliclazide	Combination (9th day)
1	3.217 ± 2.17	16.817 ± 8.3	9.950 ± 8.5
2	7.517 ± 6.53	31.962 ± 5.4	40.032 ± 5.5
3	6.759 ± 5.97	24.951 ± 5.5	31.929 ± 5.6
4	2.711 ± 3.45	19.099 ± 4.2	25.484 ± 4.2
6	6.089 ± 7.78	15.427 ± 3.1	20.342 ± 3.1
8	5.877 ± 8.08	5.651 ± 4.0	9.466 ± 4.1
12	8.766 ± 6.74	5.666 ± 2.8	7.748 ± 2.8
24	7.064 ± 4.95	4.903 ± 3.4	5.963 ± 2.1

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Table 2: Comparison of gliclazide's pharmacokinetics with and without ornidazole pretreatment

Parameter	Gliclazide	Combination (9th day)
C_{max} (µg/ml)	2.26±0.16	4.471±0.51***
AUC_{total} (µg/ml*hr)	12.95±1.68	27.53±4.47***
$t_{1/2}$ (hr)	5.98±1.8	5.58 ± 0.75^{NS}
MRT (min)	6.46±51.85	8.83 ± 31.44^{NS}
Cl (ml/ hr)	391.65±3.03	185.61±0.86***
Vd (ml)	3250.8± 873.1	1478.09±204.81**

Statistically significant at ***P<0.0001 and **P<0.0022 when compared with gliclazide control, NS- non significant. (Unpaired t test).

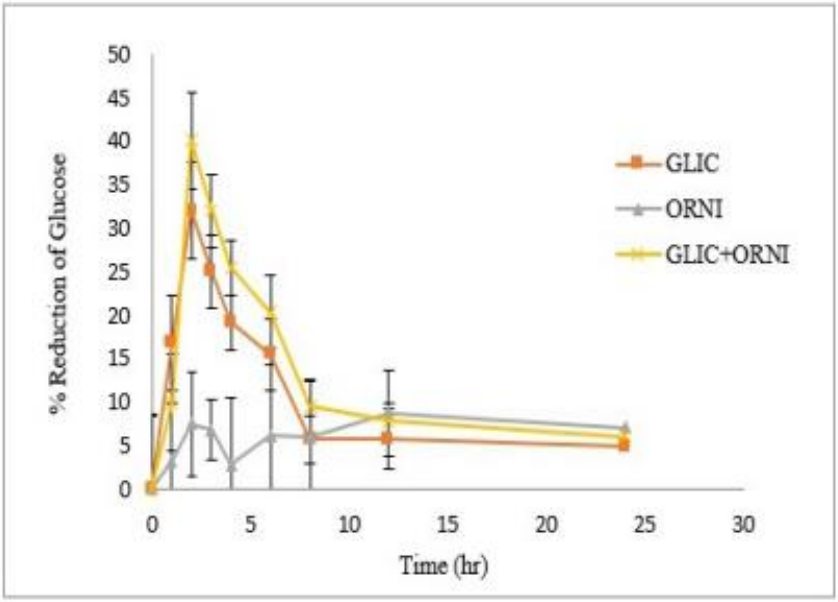

Figure 1: Glucose levels over time after taking gliclazide, ornidazole, and a combination of the two

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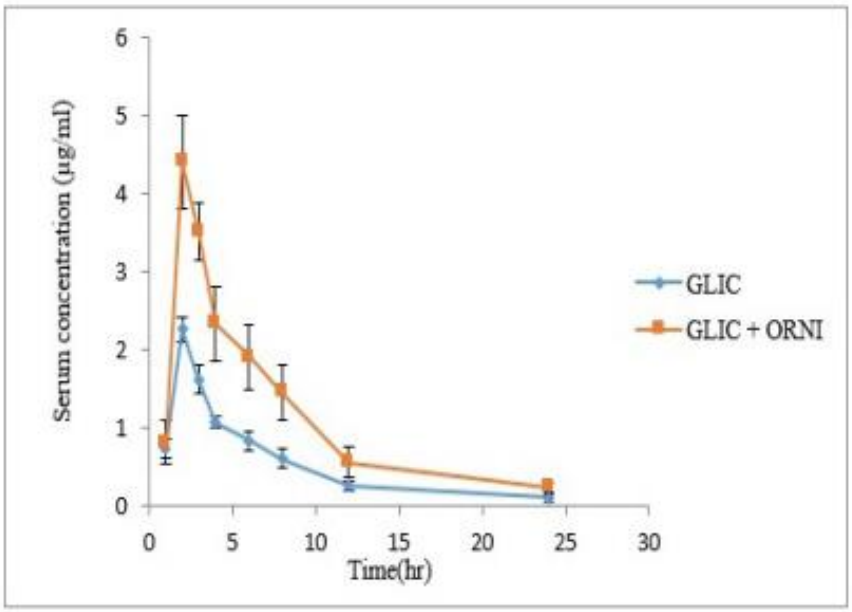

Figure 2: Time-concentration curve of gliclazide in plasma, pre- and post-ornidazole

DISCUSSION

Animal models are often used to assess the mechanism of drug interactions seen in clinical practice. The connection was rapidly identified using a healthy rat model. The effects of ornidazole on the bioavailability and elimination half-lives of gliclazide were investigated. With multidose therapy, ornidazole increased gliclazide's hypoglycaemic activity from 31.962 5.4 to 40.032 5.5 at hour 2, although this improvement was not statistically significant.

Changes in pharmacokinetic parameters were statistically significant, with increases in Cmax (by 49.4%), AUC(0-inf) (by 52.9%), and MRT (by 26.8%). Reduced by 54.5 percent in clearance and 52.5 percent in Vd. Ornidazole's ability to inhibit the CYP2C9 isoenzyme system may explain why it enhances the hypoglycemic impact of oral antidiabetic medications and raises gliclazide blood level. The interaction may occur because ornidazole blocks the enzyme responsible for metabolizing gliclazide, CYP2C9.

CONCLUSION

Ornidazole increases plasma concentration of gliclazide, which means a little dosage modification is necessary and caution should be used while prescribing the combination for their therapeutic benefit in diabetic patients. Nevertheless, further research is needed to corroborate this relationship via pharmacokinetic interaction studies in many species, since the current study is restricted in its ability to define the underlying mechanism(s) of action. There has to be research on whether or whether human beings will have a comparable interaction.

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