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Comparative study of *in vivo* effects of Glipizide and Metformin-HCl on plasma concentration of Aminophylline in healthy rats

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Abstract
The Drug Drug interactions will alter the mechanism and therapeutic efficacy of one drug either by showing Antagonistic and Synergistic Actions. In this we explain a relation between Asthma and Diabetes. Simultaneous Administration of Aminophylline with Metformin HCl does not alter the plasma drug Concentration of Aminophylline. But Administration with Glipizide shows significant changes in the plasma drug concentration of Aminophylline. This may be due to higher Affinity of Glipizide for the plasma protein. So Competitive inhibition of the binding to the plasma protein on the mixed condition can lead to hazardous consequences i,e. Competitive inhibition of the binding to the plasma protein by Glipizide Increase the plasma concentration of Aminophylline. Such Interactions of drugs can Effect the Binding of Plasma proteins & subsequently change in plasma concentration of drugs. The plasma concentration of free drug in plasma &tissues after redistribution may change in Pharmacokinetic properties of drugs.

Keywords: Drug–Drug interaction , glipizide, metformin-HCl

Introduction

Drug–Drug interaction result when one drug alters the known therapeutic response of another that has been administered concurrently or before or after the drug. The next result may be enhanced or diminished effects of one or both the drugs (Hanston and Hom, 1989). A common practice in third world is the prescription of multiple drugs at a time, which may sometimes be neither safe nor effective and may be deleterious. Over the last 10 years, the research on drug-drug interactions, drug-metal interactions and drug-food interactions was carried out by Amran *et al*. (2006a, b, 2008) [1, 2, 3, 4] and Bari *et al*. (2000) [5]. In continuation on the fate of multiple drug use the effects of glipizide and metformin on the plasma concentration of Aminophylline have been studied.

Aminophyllne is a methylxanthine that inhibits the enzyme phosphodiesterase and has an antagonistic effect on central adenosine receptors. It is a stimulant of the CNS, particularly the higher centre, and it can produce a condition of wakefulness and increased mental activity. It may also stimulate the respiratory centre, increasing the rate and depth of respiration. Aminophyllne facilitates the performance of muscular work and increases the total work, which can be performed by a muscle. Aminophyllne is used as a mild CNS stimulant in usual doses of 50 to 100 mg by mouth, although doses of up to 200 mg may be used. It is also frequently included in oral analgesic preparations with aspirin, paracetamol, or codeine in unit doses of 15 to 65 mg although its clinical benefit is debated. It is sometimes given with ergotamine in preparations for the treatment of migraine; usually in unit doses of 100 mg. Aminophyllne is absorbed readily after oral administration and is widely distributed throughout the body. It is also absorbed through the skin. Aminophyllne is metabolized almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine and other metabolites with only about 1% unchanged (Sawynok, J. 1995. Martindale: 2005 [17, 25, 26]. Glipizide is a sulfonylurea antidiabetic agent. It is given by mouth in the treatment of type-II diabetes mellitus and has duration of action of 12 to 14 hours. Glipizide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. It is extensively metabolized in the liver to metabolites that have no significant hypoglycemic activity. The metabolites and a small amount of unchanged drug are excreted in the urine (Kobayashi, K. *et al*. 1984) [9].

Concurrent administration of Aminophyllne and Metformin Hcl did not show any significant changes in plasma concentration of Aminophyllne. However that of Aminophyllne and Glipizide showed significant changes in plasma concentration of Aminophyllne. This may be due to higher affinity of Glipizide for the plasma protein. So, competitive inhibition of the binding to plasma protein on the mixed condition can lead hazardous consequences i.e, a competitive inhibition of the binding to plasma protein by Glipizide increase the plasma concentration of Aminophyllne.

Such interations of the drugs that affect the binding of plasma protein and subsequently change the plasma concentration of the drugs are very vital and to be given priority before formulating drug therapy. Since,drug displaced from plasma protein will redistribute into its full potential volume of distribution, the plasma concentration of free drug in plasma and tissues after redistribution may be change the pharmacokinetics properties of the drug and therapy may affect its pharmacological and toxic effects.(Gilman *et al*.,1991) [7] Milon and hossain (2009) [11], rahman and hossain (2008) [14] and salam and hossain (2001) [15] are engaged in The study of interaction between oral anti diabetic drugs and other agents.

In such studies, most of the agents used did not interact strongly with oral anti diabetic agents but in the present study, Glipizide increased the plasma concentration of Aminophylline. This is due to the competitive protein binding between Glipizide and Aminophyllne since the protein binding of Aminophyllne 80% and in the presence of Glipizide the protein dinding of Aminophyllne is 80% (mohiudin and hossain 2008).

The aim of present study was to evaluate the effect of Glipizide and Metformin HCL on plasma concentration of Aminophylline and thus to infer the fate of combined drug Therapies for these drugs: Glipizide, Metformin HCL, Aminophylline.

Materials and methods

20 healthy male swiss wistar rats weighing 250to300gm were acclimatized to experimental room at temperature 23+2 c, controlled humidity condition (50to55%) and 12 h light and 12h dark cycle. They were caged with a maximum of two animals in poly propylene cage and were. Fed with standard food pellets and water and libitum.all the studies conducted were approved by the institutional animal ethical committee of Aditya College of Pharmacy Research, Surampalem, According to prescribed Guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govemment of India Red. No. 1269/a/10/CPCSEA.

Results

The invivvo effects of Glipizide and Metformin Hcl on plasma concentration of Aminophylline have been studied by observing the change in plasma concentration of Aminophylline in rats in this study the plasma concentration of Aminophylline was determined by UV spectroscopic method using calibration curve after oral single administration of Aminophylline alone and with Glipizide and metformin HCL in rats (rahat *et al*. 1999, bari *et al*. 2000) [5, 13]

Table 1: Calibration curve of Aminophyllne

conc	absob1	absob2	absob3	mean	sd
5	0.267	0.267	0.275	0.269667	0.004619
10	0.481	0.481	0.482	0.481333	0.000577
15	0.706	0.719	0.746	0.723333	0.019858
20	0.981	0.982	1.022	0.995	0.023388
25	1.206	1.263	1.289	1.252667	0.042425
slop	0.04756	0.04986	0.05136	0.049593	0.001914
intercept	0.0148	-0.0055	-0.0078	0.0005	0.012437
corrl	0.999101	0.998547	0.998696	0.998961	0.000287

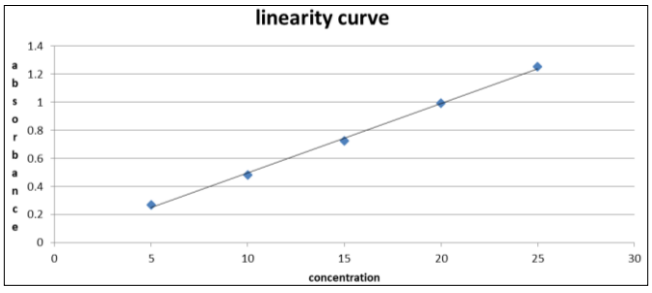

Fig 1: Calibration curve Aminophyllne

The peak plasma concentration of Aminophylline is 758.36 ug which was obtained after 7h of oral administration of Aminophylline alone.

Table 2: Single Drug Aminophylline

Time in Hours	Absorbance Max269nm	Concentration ug/ml	Amount of Drug present in 0.3ml of Plasma
0.5	0.52	1.035357	310.6071
1	0.126	2.5278	758.368
2	0.108	1.1648	649.4534
3	0.083	1.6606	498.827
4	0.071	1.4185	425.57
5	0.057	1.136204	340.8612

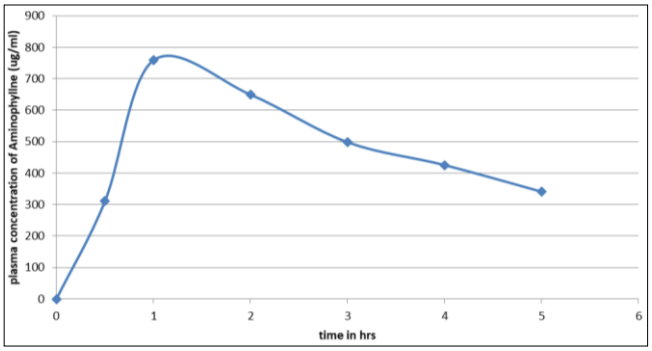

Fig 2: Plasma concentration of Single Drug Aminophylline

The oral concomitant administration of Aminophylline and Glipizide makes a significant change in plasma concentration of Aminophylline this case the peak plasma concentration of Aminophylline is 1121 g.

Which is significantly greater than that of Aminophylline when administration alone.

Table 3: Aminophylline + Glipizide

Time in Hours	Absorbance Max 269mn	Concentration ug/ml	Amount of Drug present in 0.3ml of Plasma
0.5	0.117	2.34637	703.9109
1	0.186	3.73806	1121.418
2	0.127	2.5480	764.4191
3	0.09	1.8017	540.5385
4	0.069	1.378	413.4712
5	0.043	0.8538	256.1497 3799.907

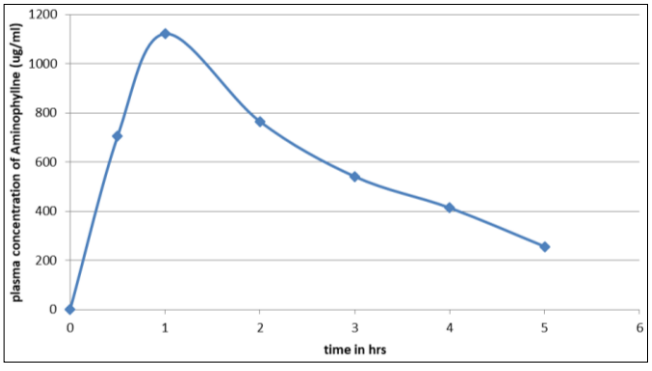

Fig 3: Aminophylline + Glipizide

The Results shown that the concurrent administration of Aminophylline and Metformin HCL does not make any change in plasma concentration of Aminophylline in this case the peak plasma concentration of Aminophyllne in this case The peak plasma concentration of Aminophyllne 933.842ug.

Table 4: Plasma concentration of Aminophylline + Metformin HCL

Time in Hours	Absorbance max269nm	Concentration ug/ml	Amount of Drug present in 0.3ml of plasma
0.5	0.077	1.5395	461.84
1	0.155	3.112808	933.842
2	0.137	2.07497	824.92
3	0.109	2.185014	655.5042
4	0.082	1.64044	492.1319
5	0.071	1.4185	425.5728 3793.856

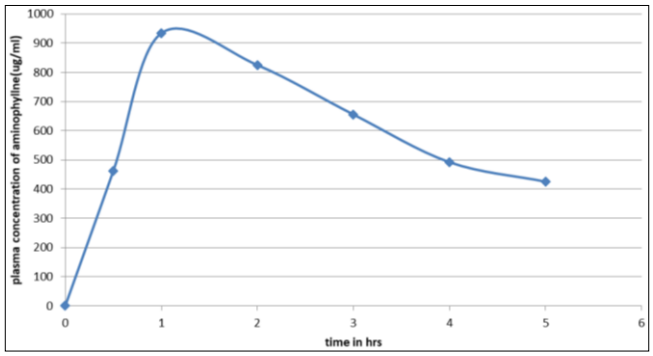

Fig 4: Plasma concentration of Aminophylline + Metformin

Table 5: Average plasma concentration of Aminophyllne after single administration

Time in hrs	Amount of Aminophyllne/0.3ml of plasm concentration of Metformin		
0	0	0	0
0.5	310.6071	706.9109	461.8778
1	758.3683	1121.418	933.8423
2	649.4534	764.4191	824.9274
3	498.1827	540.5385	655.5042
4	425.5728	413.4712	492.1319
5	340.8612	256.1497	425.5728

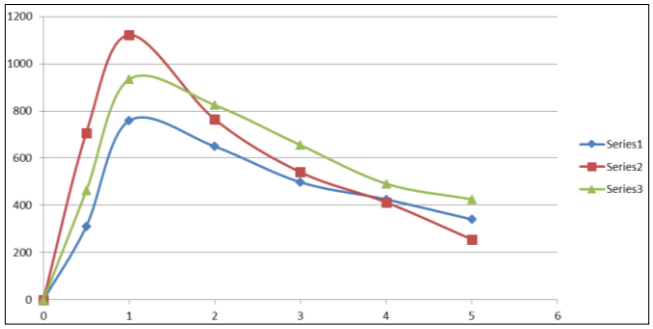

Fig 5: Average plasma concentration of Aminophyllne after single oral Administration

Discussion

A drug interaction can be defined as the modification of the effects of one drug by the other drug. The interaction can modify the drugs by forming chemical complex, nullify the action, increase the effect, decrease the effect, induce or inhibit the hepatic metabolism and elimination rate, create an environment (by changing the pH of the stomach or urine, by increasing or decreasing the sensitivity to other drugs) where the other drug failed to exert its effects. The net result may be enhanced or diminished effects of one or both the drugs (Cadwallader, D.E. 1985) [23]. A drug interaction may be pharmacokinetic or pharmacodymamic in nature. Pharmacokinetic interactions influence the deposition of a drug in the body and involve the effects of one drug on the absorption, distribution, metabolism and excretion of another. Due to large inter and intra patient variability in drug disposition, pharmacokinetic interaction seldom produces serious clinical consequences. Pharmacokinetic interactions are frequently associated with changes in plasma drug concentration and when feasible, observing the clinical status of the patients as well as monitoring serum drug levels may provide useful information about potential interactions. Pharmacodynamic interactions are related to the pharmacologic activity of the interacting drugs. These are more frequent mechanism of pharmacodynamic interactions includes synergism, antagonism, altered cellular transport and effects on receptor sites. When a drug is administered orally, it first must be dissolved in GI fluids before transport can take place across a membrane into the systemic circulation. The drug is then distributed to various parts of the body where it may be stored, metabolized, exert a pharmacological action, or be excreted. Thus a drug may come in close contact with food staffs and different body components or with another drug(s) that has been administered simultaneously, just prior to or just after itself and it may form complex with such drugs. This may be harmful or harmless. Adverse drug interactions can cause a loss in therapeutic activity, toxicity or unexpected increase in pharmacological activity of a drug arising from alteration of absorption, bioavailability and other biochemical process. Therefore, it should be known the possible interaction of a new drug when it goes to be used clinically. The study of drug interactions occupies an important place in the field of drug research, especially drug design and drug development. Such study is compulsory for the newer drugs (Gibaldi, M. 1977) [24].

Aminophyllne consumption has been extensively studied in relation to various diseases but not until recently has it been examined in relation to risk of type -2diabetes (van dam and hu, 2005) a study shows that higher Aminophyllne consumption was associated with a substantially lower risk of type 2diabetes (schaefer, 2014). On the other hand this study found a significant change in plasma concentration of Aminophyllne when Glipizide administered concurrently with Aminophyllne. Therefore, the diabetic patients who are taking Glipizide should avoid excessive consumption of Aminophyllne that contained Aminophyllne and care and monitoring might be necessary as well.

In this study determination of plasma concentration of Aminophyllne in rat by UV spectroscopic method shows that concurrent administration of Metformin Hcl does not make noticeable changes in plasma concentration of Aminophyllne but administration of Glipizide in rats showed a significant change in plasma concentration of Aminophyllne. It was observed that Glipizide lowered the affinity of protein binding of Aminophyllne hence an increase in volume of distribution of Aminophyllne might be occurred with Glipizide.

Conclusion

From this study, it was concluded that Glipizide and Metformin Hcl oral Antidiabetis Potentiates the Aminophylline action in Asthma treatment.

Combination therapy is a useful and common practice in modern medical science, where two or more drugs are administered concurrently. The results in this study have shown that Aminophyllne can enhance both Glipizide and

Metformin HCl plasma concentration in rats. The data obtained would help us to suggest that Glipizide as well as Metformin HCl may result into compatible combination therapies with Aminophyllne which is useful in the treatment of diabetic patients. However trials in higher animals and human are necessary.

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