Sildenafil Plasma Concentration:
Time Profile After Cimetidine Co-Administration

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Abstract:

To assess the plasma concentration-time profile of sildenafil alone and after a single dose (400mg) of cimetidine, with other pharmacokinetic parameters, a study was conducted at the Department of Pharmaco-logy, College of Medicine and Department of Che-mistry, College of Science, University of Mosul, from May 2008-June 2008. Twelve healthy volunteers were each given a sildenafil tablet 50 mg and blood samples were drawn at 0, 0.5, 1, 2, 4, 6, 8, 10 and 12 hours after administration. After a one week washout period, the same volunteers were given cimetidine 400 mg followed two hours later by sildenafil 50 mg and blood samples drawn at 0, 0.5 , 1,2 , 4 , 6 , 8 , 10 and 12 hours after the sildenafil administration. Using high performance liquid chromatography (HPLC) for analysis, the concentration-time profile, half-life (t1/2), area under the curve (AUC), k (elimination) were measured. Maximum plasma concentration (Cmax) and time to reach maximum plasma concentration (T max) were calculated.

Co-administration of cimetidine resulted in significantly higher plasma concentrations of sildenafil, reflected by a significant rise in AUC ($p<0.0001$) and a significant increase in C max ($p<0.0001$). The k (elimination) of sildenafil was significantly delayed ($p<0.0001$) and the elimination half-life was prolonged ($p<0.0001$).

Cimetidine through its action as an inhibitor of Cytochrome P3 A4 (the metabolic pathway of sildenafil) increases the plasma level of sildenafil as reflected by the increase in AUC, C max, t1/2 and a significant reduction in k(elimination).

Key Words: Sildenafil, serum concentration-time profile, cimetidine co-administration.

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Introduction:

Sildenafil, a potent selective inhibitor of phosphodiesterase 5 (PDES), was the first oral therapeutic agent introduced for the management of male erectile dysfunction[1]. In addition to its effect on erectile function, it can lead to vasodilation and a subsequent reduction in both systolic and diastolic blood pressure[2]. Oral sildenafil is well absorbed from the gastrointestinal tract but its systemic bioavailability is only 40% due to extensive presystemic elimination mediated primarily by the cytochrome P450 isoenzyme CYP3A4[3,4], the principle isoenzyme of sildenafil metabolism. Cimetidine, a histamine H2-receptor antagonist used in peptic ulcer disease and approved by the Food and Drug Administration (FDA) for prescription since 1979[5,6], is one of several drugs known to inhibit CYP3A4.

The aim of this study was to assess the concentration-time profile of sildenafil when given alone and the changes that cimetidine can cause on some of pharmacokinetic parameters of sildenafil.

Subjects and Methods:

Twelve healthy male volunteers aged 33.75+ 4.25 years (28-40 years) with a body mass index of 22.61+0.24 agreed to participate in the study after careful explanation. Selection criteria included, no diseases of liver or kidney, no diabetes mellitus nor hypertension, being a non-smoker, no drinking of alcohol, and on no therapy. They were instructed to avoid any drug therapy throughout the study period.

All the volunteers were given an oral first dose of sildenafil citrate tablets 50 mg. (Ajanta Pharma Ltd; India) and blood samples were drawn at 0, 0.5, 1, 2, 4 , 6 , 8 , 10 and 12 hours afterwards. Then, after a "washout" period of one week, they were given cimetidine tablets 400 mg (Ajanta Pharma Ltd; India) followed after two hours by a sildenafil 50mg tablet and blood samples were drawn at 0, 0.5, 1 , 2 , 4 , 6 , 8 , 10 and 12 hours. Food was allowed three hours after sildenafil administration.

Plasma samples were assayed using an HPLC method described by Sheu, et.al., (2003)[7].

The maximum plasma sildenafil concentration (C max), and the time to achieve C max (t max) were determined

directly from the individual concentration-time profiles. The elimination rate constant (K) was determined for each individual from log-linear regression of a plasma concentration-time curve during the elimination phase. The elimination half-life (t1/2) was determined as 0.693/k.

The area under the curve (AUC 0-t) was determined by the linear trapezoidal rule and the AUC t-a was determined as the last observed concentration divided by k elimination, and the total AUC-0-a was determined as the sum of AUC0-t and AUCt-a. All volunteers were carefully monitored for any reported adverse effects or changes in blood pressure. Two of the 12 volunteers experienced severe headache and hypotension.

Statistical Analysis:

Results were quoted as mean+SD. Comparison between results of measured parameters was done using paired t-test. $P < 0.05$ was considered significant.

Results:

Co-administration of cimetidine 400mg as a single dose with a sildenafil 50mg tablet resulted in a significant raise in plasma sildenafil concentration **(Figures 1, 2)**. This was reflected by the significant increase ($p<0.0001$) in the AUC from 1555+311 µg.h/l to 3281+587 µg.h/l, and a significant rise in C max ($p<0.0001$) from 241.66±25.16µg /l to 520+22.56 µg /l. The elimination of sildenafil was also reduced significantly ($p<0.0001$) from 0.271+0.035 h-1 to 0.204+0.017 h-1 and the elimination half life was prolonged significantly ($p<0.0001$) from 2.59+0.39h to 3.41+0.28h **(Table 1)**.

Co-administration of cimetidine with sildenafil did not affect significantly the rate of sildenafil absorption as it is reflected from the insignificant differences in t max. The effect of co-administration of cimetidine and sildenafil, on sildenafil AUC, C max and k elimination may indicate that this is a clinically important and significant interaction.

Figure 1: Sildenafil plasma concentration-time profile of a single dose of sildenafil 50 mg alone

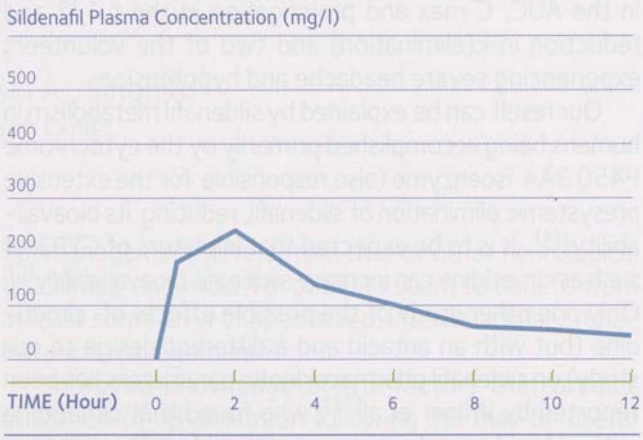

Figure 2: Sildenafil plasma concentration-time profile of a single dose of sildenafil 50 mg with cimetidine 400 mg

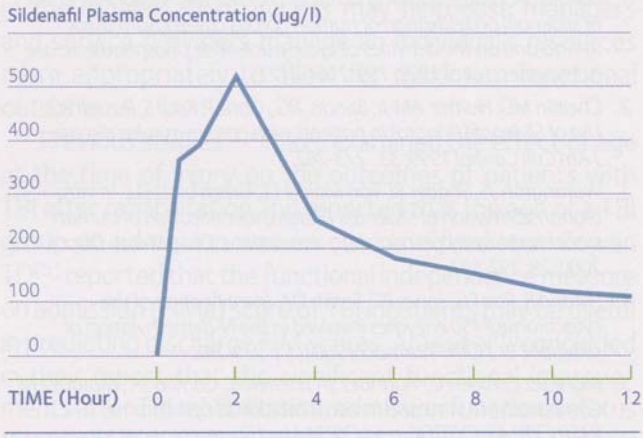

Table 1: The effect of cimetidine co-administration on sildenafil pharmacokinetic parameters

t 1/2(h)	K (h-1)	t max (h)	C max (µg/l)	AUC 0-a (µg. h/l)	Therapy
2.59+0.39	0.271±0.035	2.02+0.23	241.66+25.16	1555+311	Sildenafil alone
3.41+0.28*	0.204+0.017*	2.02+0.25	520+22.56*	3281+587*	with cimetidine

* Highly significant differences ($p<0.0001$)

Discussion:

Sildenafil was synthesized and studied originally for use in hypertension and angina pectoris but the researchers noted little effect on angina but marked penile erections[8]. The drug is effective also in the rare pulmonary arterial hypertension, Raynaud's phenomenon and altitude sickness[8,10]. It is very important to ensure the safety of this drug in a variety of conditions and to study the potential drug-drug interactions especially with commonly used drugs such as cimetidine.

The current study was performed to investigate the possible interaction between sildenafil and cimetidine,

since cimetidine is a well-known inhibitor of cytochrome CYP3A4, the major cytochrome P450 isoform responsible for sildenafil metabolism[11]. Cimetidine co-administration with sildenafil resulted in a significant rise in plasma sildenafil concentration as reflected by the rise in the AUC, C max and prolongation in the t 1/2 and reduction in k(elimination) and two of the volunteers experiencing severe headache and hypotension.

Our result can be explained by sildenafil metabolism in humans being accomplished primarily by the cytochrome P450 3A4 isoenzyme (also responsible for the extensive presystemic elimination of sildenafil, reducing its bioavailability)[4]. It is to be expected that inhibitors of CYP3A4 such as cimetidine can increase sildenafil bioavailability[6]. Only one other study of the possible effects of cimetidine (but with an antacid and a different design to our study) on sildenafil pharmacokinetic parameters has been reported by Wilner et al[12], who found that cimetidine with antacid co-administered with sildenafil resulted in a significant rise in AUC and C max of sildenafil which is in agreement with our findings, although, in contrast to our results, they reported no statistically significant effect on the K(elimination) of sildenafil. Hedaya et al[13] reported that ciprofloxacin and clarithromycin (both of which are known inhibitors of cytochome P450CYP3A4) co-administered with sildenafil resulted in a significant rise in AUC and C max of sildenafil. Muirhead, et.al., reported that the anti-human immunodeficiency viral infection (HIV) agents saquinavir and ritonavir (both of which are known inhibitors of cytochrome P450 CYP3A4) co-administrated with sildenafil resulted in a significant increase in sildenafil bioavailability and slowed its elimination[1]

Conclusion:

This could be the first study which demonstrated that co-administration of cimetidine with sildenafil resulted in a significant rise in sildenafil plasma concentration as reflected by the significant rise in AUC, C max and the prolongation of t 1/2 and the reduction in k(elimination). This should be monitored carefully, especially in patients with severe cardiovascular diseases and those who are on organic nitric or antihypertensive agents.

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