THE INFLUENCE OF VERAPAMIL ON THEOPHYLLINE SERUM CONCENTRATIONS

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SUMMARY

The effect of verapamil on steady state levels of theophylline were studied in 10 healthy volunteers. Sustained release theophylline 3 mg/kg/day was administered 3 days prior to, and during a 7 day treatment of verapamil 80 mg three times daily. Steady state theophylline levels were measured before giving verapamil and on days 3, 5, and 7 of verapamil. Blood for theophylline assay was drawn one hour before the morning theophylline dose. The results showed no statistically significant difference in theophylline levels before and after verapamil. We conclude that oral verapamil does not affect the disposition of oral theophylline at the dose studied.

I. INTRODUCTION

Verapamil is a calcium channel antagonist useful in the treatment of angina pectoris, supraventricular tachyarrhythmias, and hypertension. Since verapamil's release in the United States, a variety of drug interactions have been reported with verapamil. These include elevation of digoxin, carbamazepine, metoprolol, quinidine, and cyclosporin serum levels with concomitant verapamil administration /1-5/.

Verapamil interferes with the metabolism of antipyrine which is a marker of drug metabolism via cytochrome P-450 system /6-7/. Since cytochrome P-450 is thought to be responsible for the metabolism of theophylline /8/, it is possible that verapamil could cause an increase in theophylline serum levels. This possible interaction is supported by a case report which describes doubling of theophylline serum levels associated with verapamil therapy /9/. Theophylline and verapamil may be coadministered frequently since many patients with pulmonary disease may also have coexisting angina or supraventricular arrhythmias. This is especially true for multifocal atrial tachycardia for which verapamil may be effective /10/. The purpose of this study was to assess the effect of verapamil administration on steady state serum levels of theophylline.

II. METHODS

Thirteen healthy subjects between the ages of 23 to 30 volunteered to participate in the study after giving written informed consent. The study was approved by the Institutional Review Board. Subjects were not allowed to take any drugs which may influence the disposition of theophylline during the study. None of the subjects smoked cigarettes. Subjects were instructed to maintain their usual dietary habits during the study. No specific dietary restrictions were made.

Sustained release theophylline (Theodur: Key Pharmaceuticals) was administered for a total of 10 days. The dose of theophylline was 3 mg/kg per day given in two divided doses at approximately 9am and 9pm. The dose of theophylline was rounded off to the nearest 100 mg per day. Theophylline levels were drawn at approximately 8am on days 3 and 4 of the study to assess steady state conditions. Verapamil 80 mg

three times a day was administered starting on day 4 and continued for the next 6 days. Repeat theophylline serum levels were measured at 8am (before the morning theophylline dose) on days 7, 9, and 11 of the study. The last theophylline and verapamil dose was administered at approximately 9pm on day 10 of the study.

Samples collected on a daily basis were batched and assayed in a single run. Serum levels were analyzed for theophylline by fluorescence polarizaiton immunoassay (TDX: Abbott Laboratories). The coefficient of variation of this assay is 2.8% at a concentration of 7mcg/ml. The baseline serum theophylline concentrations were compared to theophylline levels while taking verapamil. Analysis was performed using a repeated measures ANOVA. An alpha level of 0.05 or less was considered statistically significant (two tailed test). All data are reported as the mean +/- one standard deviation.

III. RESULTS

Ten of the thirteen subjects completed the protocol. Three subjects dropped from the study before verapamil was administered due to intolerable side effects of theophylline.

Theophylline serum concentrations are present in Table 1. There was not a statistical difference between the theophylline levels before verapamil and while on verapamil for any day tested. There was a slight trend for an increase in theophylline level on day 3 of verapamil but this difference was not statistically significant.

V. DISCUSSION

Verapamil has been reported to alter the disposition of several drugs. Since verapamil also inhibits the metabolic clearance of antipyrine, an interaction with theophylline could be anticipated. However, our study does not support verapamil significantly increasing theophylline serum levels at steady state. Our data are consistent with those reported by Robson et al. who reported a small decrease in clearance of theophylline (14%) with concomitant verapamil use /11/. Sirmans et al. demonstrated an 18% decrease in theophylline clearance with verapamil administration /12/. In that study larger doses of both theophylline and

TABLE 1.

Theophylline serum concentrations (mcg/ml) before and during verapamil administration

Subject	Day -1	Day 0	Day 3	Day 5	Day 7
1	6.7	6.6	7.5	6.8	6.6
2	3.6	3.8	4.0	4.0	4.1
3	4.8	5.5	7.4	7.6	6.5
4	6.9	7.2	8.5	7.6	5.1
5	5.8	7.0	6.0	5.4	6.0
6	3.2	3.2	5.2	3.7	2.7
7	5.8	4.4	5.3	5.2	4.7
8	6.1	6.1	5.6	6.5	5.0
9	4.2	3.5	5.0	4.4	6.3
10	8.9	8.6	9.0	10.0	11.0
mean	5.6	5.5	6.3	6.1	5.8
S.D.	1.7	1.8	1.6	1.9	2.2

verapamil were used which could explain the difference in results between theirs and this study. It is unknown if larger doses of theophylline in our study would have resulted in a statistically significant interaction. The small dose was selected for this trial since numerous side effects were encountered with larger doses before verapamil administration. It is possible that interference of absorption of theophylline by verapamil may occur which may influence our results.

We conclude that verapamil at the dose studied does not influence serum concentrations of theophylline when administered orally. Further studies are needed to support our findings.

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