

Drug Interaction 1

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Drug Interaction: Diltiazem and Cyclosporine

The mechanism of action and pharmacokinetic profile of each drug

Diltiazem

The class of medications that diltiazem belongs to is known as calcium-channel blockers. The use of the drug is for controlling angina (chest pain), and the treatment of high blood pressure. Other than relaxing the blood vessels to reduce the stress on the heart, diltiazem also increases the heart's supply of oxygen and blood.¹ The drug enhances premature diastolic ventricular relaxation on the left in hypertrophic cardiomyopathy. The functioning of diltiazem reduces systolic calcium entrance into automatic and myocardial cells, and while in the heart it binds L-type calcium channels. Diltiazem prevents coronary artery spasms provoked by ergonovine and spontaneity. For normotensive individuals, the drug brings about a modest fall in blood pressure and a reduction in peripheral vascular resistance.

Cyclosporine

Cyclosporine treats a variety of autoimmune and inflammatory diseases and prevents rejection of organ transplant through its immunomodulatory properties. As a calcineurin inhibitor, the drug prevents the activation of T-cells. The drug binds with cyclophilin-1 receptors in the cells to form complex cyclosporine-cyclophilin². The resulting complex is the source of inhibition for calcineurin, and for the activated T-cells it consequentially halts the activation and dephosphorylation of the nuclear factor responsible for inflammatory reactions. Oral absorption of cyclosporine is slow and incomplete and the drug is highly lipophilic. The range of cyclosporine bioavailability ranges from 10% - 89%. The distribution of the drug is between 3 to 5 L/kg, which is extensive in peripheral tissues. ² In plasma, cyclosporine primarily binds itself lipoproteins and secondarily to albumin³.

Basis of the interaction

Co-administration of diltiazem and cyclosporine increases the blood concentration of cyclosporin A (CyA), and metabolites 17 and 18 of CyA. However, the metabolites 1 and 21 did not increase. A week of administration of the two increased the mean whole body CyA trough level from 117ng/ml to 170ng/ml⁴, as determined by HPLC. A similar increase was observed for metabolite 17 from 184ng/ml to 336ng/ml. The effect of diltiazem was probably from non-competitive inhibition of CyA-metabolism by the drug. However, the increased concentration of metabolite 17 may have been brought about by secondary inhibition of secondary metabolism steps.

Clinical consequence(s) of the interaction, including adverse or toxic effects, therapeutic failure, or some other clinically relevant outcome, and why these consequences occur.

Diltiazem in lower doses has few adverse effects. The safety consideration is the reason why the dosage is lower than the permissible levels to allow a significant reduction in the treatment of cyclosporine. The low dose of diltiazem enables the use of the drug in situations that it has been previously hitherto contra-indicated.

Appropriate recommendation to minimize or avoid the interaction.

There are significant variations between patients in any study, which necessitates individualized monitoring of blood cyclosporin before and after introducing diltiazem. Prior control should take account of the trough blood CsA concentration or CsA AUC, particularly for patients whose diltiazem dose is primarily for economic benefit. After each dose increment, a preferable stabilization period is two weeks after which the concentrations should be measured again. The recommended initial dose of diltiazem should 30 mg, whose increment will go to 60mg mane, then 60mg twice in a day⁵. However, the increments should be based the magnitude

of response and clinical situation of the patient. The administration of diltiazem should be concurrent with CsA doses. However, diltiazem should be discontinued if no observations indicate an increase in CsA concentrations and no clinical indication for diltiazem.

References

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