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DRUG-DRUG INTERACTIONS (CYP 450)

Many adverse drug-drug interactions are attributable to pharmacokinetic problems and can be understood in terms of alterations of P450-catalyzed reactions. The three major drug-drug interactions involving P450s are inhibition, induction and possibly stimulation.

A relatively small subset of the total number of human P450s appears to be responsible for a large fraction of the oxidation of drugs. I will focus on one group of drugs which is well prescribed to elderly subjects - benzodiazepines (BZD).

Diazepam, nitrazepam, alprazolam, estazolam, midazolam and triazolam are all substrates for CYP3A4 - the most active isoform of all CYP450 forms. The activity of CYP3A4 is inhibited by antidepressants (fluoxetine, norfluoxetine, citalopram, paroxetine, sertraline); antibiotics (ciprofloxacin, clarithromycin, erythromycin) but also by different substances as: verapamil, diltiazem, nifedipine, valproic acid, cimetidine, bromocriptine, grapefruit juice. On the other hand the activity of CYP3A4 can be induced by i.e. carbamazepine, phenobarbital, phenytoin.

It is proven that concomitant use of BZD and substances that inhibit CYP3A4 activity lead to high plasma concentration of BZD and to excessive patient's sedation. Such drug-drug interaction can be extremely dangerous in the elderly because of pharmacokinetics and pharmacodynamics changes in the metabolism of BZD. As we get older the volume of distribution and the half-life of BZD is increasing so there is great risk of cumulation and intoxication, especially if long-lasting benzodiazepines that undergo through the first stage of liver metabolism i.e. diazepam or nitrazepam are used. Therefore the alternatives for these BZD would be i.e. oxazepam which undergo only through the second stage of liver metabolism.

On the other hand if BZD are used concomitantly with the substances that induce CYP3A4 activity the plasma concentration of BZD can be insufficient for the therapeutic effect in consequence the dose of BZD can be elevated. This situation can be dangerous when the therapy with CYP3A4 inducer is stopped but the dose of BZD remain unchanged.

It seems that understanding of the mechanism of the interactions between drugs and the system and estimating the risk of drug-drug interaction is essential to predict potential advantages and disadvantages of the pharmacotherapy and should be always done when the patient is on a few drugs concomitantly.

Short bibliography:

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- 3) Guengerich FP: Role of cytochrome P450 enzymes in drug-drug interactions. *Adv. Pharmacol.* 1997, 43:7-35

