



PIC QUESTION OF THE WEEK: 8/27/07

Q: What are some of the potential drug interactions associated with tramadol?

A: Tramadol is a synthetic analgesic that is structurally similar to codeine. Both the parent compound and its active metabolite, O-desmethyltramadol (M1), provide analgesia by stimulating mu-opioid receptors. In addition, tramadol serves as a weak inhibitor of norepinephrine and serotonin reuptake. Tramadol exists as a racemic mixture and the metabolism and action of both enantiomers must be considered when evaluating potential drug interactions and/or adverse reactions. The parent compound is metabolized by the enzyme CYP2D6 to M1; therefore, agents that inhibit CYP2D6 can increase serum tramadol concentrations while decreasing levels of M1. Drugs such as amiodarone, haloperidol, propoxyphene, propafenone, etc. inhibit CYP2D6. Differences in genetic makeup can affect the activity of this enzyme. Co-administration of these and similar compounds may reduce the analgesic efficacy of tramadol. Although tramadol has less potential for producing CNS depression than opiates, the effect is still possible, especially if the drug is combined with CNS depressants such as carbamazepine, opiate agonists, neuroleptics, anxiolytics, etc. The risk of serotonin syndrome is increased when tramadol is administered in combination with other serotonergic agents, including: selective serotonin reuptake inhibitors (SSRIs); serotonin norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine; and the monoamine oxidase inhibitors (MAOIs) phenelzine and tranylcypromine. The simultaneous use of tramadol and MAOIs or the use of tramadol within 14 days of discontinuing an MAOI is included in the *warning* section of its package insert. The product literature of the selective MAOI rasagiline (Azilect) includes a contraindication against combined use with tramadol. Agents that possess some MAO inhibitory activity (e.g. linezolid and procarbazine) should also be used cautiously if administered with tramadol. Seizure threshold can be decreased by tramadol. Combining the drug with agents capable of producing the same effect can increase the risk of seizures. These compounds include antidepressants affecting serotonin reuptake (SSRIs and some tricyclic antidepressants), cyclobenzaprine, opiate agonists, naloxone, anti-psychotic compounds, anorexic agents, etc. A decrease in seizure threshold may also interfere with the ability of anticonvulsants to control seizures. The R-enantiomer of tramadol is partially metabolized by the CYP3A4 isozyme and it would be expected that inhibitors of CYP3A4 (e.g. ketoconazole, erythromycin, etc.) could result in increased concentrations of tramadol. Because of its complex mechanism of action, pharmacogenomic-related metabolism, and ability to affect seizure threshold, caution should be exerted when administering tramadol with other drugs. Fortunately, significant drug interactions with tramadol appear to be infrequent.

References:

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