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Tramadol Extended-Release Tablets

A Viewpoint by Mellar P. Davis

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Tramadol is a dual-action opioid, which inhibits monoamine reuptake and through its major metabolite, *O*-desmethyltramadol (M1), is a μ-receptor agonist.[1] M1 is derived from cytochrome P450 (CYP) 2D6.[2] Tramadol is enantiomeric; (−)-tramadol inhibits noradrenaline reuptake and (+)-tramadol inhibits serotonin reuptake.[3] Most analgesia is derived from interaction with μ-receptors and $\alpha 2$ adrenoceptors.[4] However, even poor metabolisers will derive some analgesic benefit from tramadol.[5]

The dose proportionality of tramadol suggests no limits to its bioavailability. No evidence exists for analgesic tolerance, at least over 12 weeks. The kinetics of tramadol are altered by significant hepatic and renal failure.[1] Immediate-release (IR) tramadol (the standard formulation) becomes kinetically extended-release tramadol when renal or hepatic failure is severe.[1] Tramadol IR should be avoided altogether in organ failure. Steady-state levels are reached by day 4–5; hence, the around-the-clock dosage should not be increased for 4–5 days after initiating extended-release (ER) tramadol in order to avoid delayed toxicity.

Tramadol ER will increase patient compliance as a result of once-daily administration. In addition, tramadol is not associated with renal failure or gastrointestinal bleeding, as are NSAIDs. There is little legal scrutiny with prescribing of tramadol, although addiction can occur. Tramadol is an effective analgesic in neuropathic pain. The number needed to treat for benefit value is 3.8, which matches the benefits of gabapentin.[5]

Toxicity is similar to that of other opioids, although confusion and myoclonus appear to be less frequent than with potent opioids. The increased risk for falls in the elderly with tramadol (1.54; 95% CI 1.49, 1.58) matches the relative risk of morphine (1.47; 95% CI 1.37, 1.58).[6] Tramadol-induced serotonin reuptake inhibition is probably the reason for early emesis.[7] Tramadol should not be given with other serotonin transport inhibitors (tricyclic antidepressants, selective serotonin reuptake inhibitors, or selective norepinephrine serotonin reuptake inhibitors) since there is an increased risk of the serotonin syndrome with the combination.[1]

Tramadol has a role in the management of neuropathic pain and chronic non-malignant pain. It is probably the 'weak' opioid of choice for cancer pain. Those individuals with an opiophobia are likely to prefer tramadol to low doses of morphine. Drug interactions can be a problem but should not deter physicians from using tramadol ER. ▲

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