Journal Watch

Tramadol in the Treatment of Neuropathic Cancer Pain

Presented by: Kathryn Andrusky, Family Medicine Resident, Grey Nuns Tertiary Palliative Care Unit during rounds on February 7, 2008

Arbaiza, Daniel and Vidal, Oscar; *Clinical Drug Investigations* 2007; 27 (1): 75-83

Tramadol is an atypical opioid analgesic with dual action – weak affinity for opioid Mu receptor and inhibition of serotonin and noradrenalin reuptake. This paper quotes several other studies, citing that "its use in chronic cancer and non-cancer pain is well established" and other studies using tramadol for non-cancer neuropathic pain.

- type of study: prospective, matched-pair, double-blind, placebo-controlled study
- investigators with the National Cancer Institute Neuro-Oncology Service in Lima, Peru
- no conflicts of interest for either author; Grunenthal Laboratories in Peru supported study by supplying the drugs, no other support/funding received

- inclusion criteria
    - Age between 18 – 60 year old
    - Histologically proven cancer
    - Cancer or cancer-treatment related neuropathic pain of moderate-severe intensity and with duration of >/= 3 months prior to onset of study
- exclusion criteria
    - Patients unable to provide adequate information about their pain
    - Patients having mainly somatic, visceral or sympathetically-maintained pain
    - Patients scheduled for surgery, radiotherapy, chemotherapy or hormone therapy
    - Use of TCAs, Tramadol or any opioid
    - Change in dosage of any antiepileptic analgesic treatment within 30 days before study
    - COPD or intracranial hypertension
    - Dependency on alcohol, analgesics or other drugs; history of psychiatric illness

- Calculated 18 patients per group were needed for confidence level of 95% and statistical power of 80%
- Patients were placed within a group in pairs, based on clinical characteristics (same pain syndrome) ,and then randomly assigned via computer to either placebo or tramadol
- Pain syndromes (and number of pairs)
    - Tumor-related plexuspathy (5)
    - Pain syndrome following surgery (4)
    - Chemotherapy-induced neuropathy (3)
    - Tumor-related epidural compression (3)
    - Entrapment of peripheral nerve by tumour mass (2)
    - Pain following herpes zoster (1)
- Investigators and patients were both blinded – medication and placebo were supplied with drops in identical 10 mL bottles
- Patients were randomized to Tramadol, received initial dosage of 1 mg/kg every 6 hours; pts were permitted to continue antiepileptic analgesic therapy and reduce dosage according to pain reduction

- Assessment at baseline, day 15, day 30 and day 45

- Pts having >/= 50% pain relief continued at same dosage; in those that didn't, dosage increased to 1.5 mg/kg every 6 hours
- Assessment tools (7)
    - Pain intensity (10 point scale)
    - Karnofsky scale (like PPS)
    - General body functions – ADLs altered by pain
    - Zung Depression Scale
    - Beck Anxiety Inventory
    - Neurophysiological studies – somatosensory evoked potentials to quantify any damage to peripheral nerves
    - Reduction in amount of antiepileptic analgesics
- Adverse effects were recorded in terms of intensity and ranked in terms of likelihood adverse effect associated with treatment; patients with severe or grave adverse event were retired from the study

- 36 patients were enrolled
- All patients completed second and third assessments (days 15 and 30); 11 patients withdrew before fourth assessment (day 45) – 6 in placebo and 5 in Tramadol (8 withdrew due to lack of analgesia – 6 in placebo and 2 in Tramadol; 3 in Tramadol group withdrew due to severe vomiting)

- Results
    - Pain intensity – reduction by 57% in Tramadol and 39% in placebo ($p<0.001$)
    - Reduction in antiepileptics – difference 'significant' ($p<0.05$)
    - Karnofsky score – improvement 10.6 tram, 6.95 placebo ($p<0.001$)
    - No difference in depression/anxiety scales or neuroconduction tests
    - General improvement sleep and ADLs; worse appetite in both groups, with placebo showing more deterioration than Tramadol group
    - Adverse effects – 67% in Tramadol and 22% in placebo
- Author's conclusions – improvement in pain symptoms in Tramadol group, were greater than in placebo; no change in mood or neurophysiological assessments , demonstrated that changes in pain therefore to were due to analgesic effect of drug

- Strengths of study
    - Well-defined, reasonable inclusion/exclusion criteria
    - Double-blinded
    - Took additional step of splitting neuropathic pain into separate pain syndromes
- Weaknesses of study
    - Authors identified a lack of titrating protocol or adjuvants to reduce adverse effects and make tramadol more tolerable
    - Small sample size (36 patients)
    - No analyses via intention to treat (despite losing almost 1/3 of participants)
    - Analysis (and p-values) not clearly explained, nor were study numbers/values included for readers to repeat analysis (particularly reduction in antiepileptics)

Relevance to palliative care – neuropathic pain is a challenging symptom to manage and Tramadol may be an additional medication to consider when treating cancer-related neuropathic pain. Further studies need to be completed to further investigate the usage, dosing and side effects of tramadol for neuropathic cancer-related pain.