

The Clinician

The Outcome Resources Drug Information Newsletter



JCAHO's National Patient Safety Goal on Anticoagulation: How Does This Affect My Hospice ?

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The Joint Commission has released a set of standards for quality improvement in home health care. National Patient Safety Goals are an integral part of these new standards. One of the goals related to improving the safety of using medications is titled, "Reducing Harm From Anticoagulant Therapy". At Outcome Resources we have fielded questions from many hospices wondering how this national safety goal on anticoagulant therapy may impact the way they care for patients who are receiving anticoagulant therapy.

The Joint Commission requirement for anticoagulant therapy states that this requirement applies only to organizations that "provide anticoagulation therapy". The first question to ask regarding applicability of this requirement is: Does my hospice provide anticoagulant therapy ?

If employees of your hospice organization are directly involved in the dispensing or administration of anticoagulants, then your hospice is considered to be a provider of anticoagulant therapy. A hospice that has an ownership stake in a pharmacy or employs a pharmacist that dispenses anticoagulant medication to the hospice may be considered to be an anticoagulant provider. If hospice nurses are directly involved with administering anticoagulant medications to their patients (as opposed to the family members), the hospice would also be considered a provider of anticoagulant therapy.

For a hospice which does not have their own pharmacy and whose nursing staff do not directly administer anticoagulant medications to their patients, the National Patient Safety Goals, technically, do not apply.

A clear definition of anticoagulant therapy is the first step for hospices seeking to comply with the goals. According to the Joint Commission, anticoagulant therapy includes only the following medications: Warfarin (Coumadin), Heparin, and the low-molecular weight heparins (Lovenox, Innohep, and Fragmin). Antiplatelet drugs such as Aspirin, Aggrenox, and Plavix are not included in the Joint Commission's National Patient Safety Goals. Once the organization has a clear understanding of which medications are to be addressed in the goal, the hospice should develop a six point plan for implementation and compliance.

The hospice's plan should address these six action points:

- 1) Develop a written anticoagulation program based upon current best practices
- 2) Provide education to hospice staff regarding anticoagulation therapy
- 3) Educate families w/ appropriate information about anticoagulant therapy
- 4) Establish lab monitoring guidelines
- 5) Establish guidelines for timely follow-up with physicians regarding lab results
- 6) Evaluate the anticoagulant program annually in a roundtable meeting format.

Outcome Resources clinical pharmacists are available to assist you in plan development.

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Plavix Drug Interactions with PPIs Revisited

Earlier this year in our January 2009 edition of The Clinician, we alerted our readers to a potential problem with Plavix (clopidogrel) and the concomitant use of proton-pump inhibitors (PPIs) such as Prilosec. At that time the FDA had issued an announcement that it was looking into a potentially significant drug interaction and had asked the manufacturer of Plavix, Sanofi-Aventis, to perform more studies. The FDA expressed concern at that time that the PPI drugs may inhibit the effectiveness of Plavix, exposing the patient to increased risk for stroke or MI. This drug interaction has very high clinical significance because of the widespread use of Plavix and PPIs in combination. PPI's are currently *recommended* in guidelines published by many professional organizations to treat or prevent peptic ulcers and gastric bleeding in patients taking Plavix and other antiplatelet drugs. The continued use of antiplatelet drugs, such as Plavix, in a hospice patient remains controversial since the drug is not considered palliative, however, it may be beneficial for some patients depending upon current quality of life, goals of care, and prognosis.

Proton-pump Inhibitors (PPIs)

Omeprazole (Prilosec, Prilosec OTC)

Esomeprazole (Nexium)

Lansoprazole (Prevacid)

Dexlansoprazole (Kapidex)

Pantoprazole (Protonix)

Rabeprazole (Aciphex)

In May of this year a large retrospective cohort study, known as the Clopidogrel Medco Outcomes study, was presented at the annual meeting for the *Society of Cardiovascular Angiography and Interventions* in Las Vegas, Nevada. This study covered more than 16,700 patients who received Plavix. It was designed to assess the impact of combining Plavix with a PPI upon the risk of major adverse cardiovascular events. This is the largest study to date looking at this drug interaction. Approximately 9800 patients received Plavix for 1 year without PPI therapy and approximately 6800 patients received Plavix for 1 year plus a PPI medication. All patient's medication status was correlated to any history of hospitalization for stroke, TIA, or related cardiovascular event. The results of this study are very interesting & should capture the attention of all

clinicians as well as the FDA.

The lead investigator, Dr. Erick Stanek, concluded that the one-year risk of major cardiovascular events is increased by more than 50% in patients taking a proton-pump inhibitor (PPI) with Plavix as compared to patients on Plavix without taking a PPI.

Dr. Stanek also looked at individual PPIs to try and determine if there is a difference in risk for this interaction from one PPI to another. His results indicates that each of the PPI's were associated with a clinically significant risk for major cardiovascular events. These results reinforce the hypothesis that this interaction with Plavix is a class effect that occurs with all PPIs.

It is believed the PPIs inhibit an enzyme (CYP2C19) that is necessary to convert Plavix to its active form in the body, essentially rendering it ineffective for its intended antiplatelet indication.

Our January 2009 article in The Clinician also suggested that histamine-2 antagonists (H2 Blocker drugs) such as Ranitidine (Zantac) or Famotidine (Pepcid) may be reasonable alternatives to the PPIs for reducing the risk of ulceration and gastric bleeding in patients taking Plavix. Dr Stanek affirmed our guidance in his presentation when he reported that his data showed no effect of these H2 blocker drugs on increasing cardiovascular events in patients taking Plavix.

In response to the accumulating evidence suggestive of a significant drug interaction between Plavix and the PPIs, The European Medicines Agency (EMA), has recommended that the product information for Clopidogrel (Plavix) be amended to discourage the concomitant use of PPIs unless absolutely necessary. In the U.S., our FDA has not issued any directives for changing the Plavix product information so far.

Some cardiologists have voiced concerns that this interaction has been given too high of a profile by the regulatory agencies. They cite some conflicting study results and indicate possible compounding factors that may skew the results. One specific criticism is that the majority of the patients who were taking the combination of Plavix plus a PPI were older and therefore may have been at greater risk for a major cardiovascular event as a result of age. Based upon this latest study, it appears that there is compelling evidence of a significant drug interaction which may have very negative outcomes. Considering the fact that we have reasonable alternative medications available (H-2 blockers) to manage or prevent Plavix induced gastric ulceration and bleeding, there is little reason to continue to use PPIs along with Plavix in most patients. In certain patients the use of PPIs may still be indicated at the direction of the gastroenterologist.

Tapentadol: New Analgesic Approved

Approved last November by the FDA, Tapentadol has finally been released for use after a lengthy process by the DEA to determine the controlled substance classification for this new analgesic. Tapentadol is indicated for management of moderate to severe pain and has been classified as a schedule II drug (similar to morphine, oxycodone, and other strong opioids). The brand name is *Nucynta*. This drug has a dual mechanism of action for achieving pain relief. It is a *mu* opioid agonist similar to other opioids currently available, however, it also has significant norepinephrine re-uptake inhibition. Nor-epinephrine re-uptake inhibition has been shown to be advantageous in various types of neuropathic pain. Norepinephrine re-uptake inhibitors such as the tricyclic antidepressants are known to increase the effectiveness of opioids in the management of neuropathic pain.

Tapentadol shares some similarities with the analgesic Tramadol (Ultram), which has been available since 1995 as an effective drug for management of moderate to moderately severe pain. Like Tapentadol, Tramadol also has a dual mechanism of action. Tramadol activity includes *mu*-opioid agonist action plus norepinephrine and serotonin re-uptake inhibition. Pain studies conducted in animals indicate that Tapentadol potency falls somewhere between that of Tramadol and Morphine.

Tapentadol was studied in placebo controlled trials in various different patient groups including post-op foot surgery patients, osteoarthritis patients with knee or low back pain, and end-stage joint disease patients; all with levels of moderate to severe pain. The studies demonstrated that Tapentadol offers pain relief and was generally well tolerated.

Potential common side effects are similar to what one would expect from an opioid medication, including: nausea, vomiting, dizziness, constipation, and sedation. Clinical trials have indicated that the incidence of side effects with Tapentadol were generally less than with equianalgesic doses of oxycodone or morphine; specifically less nausea and less dizziness. Sedation with Tapentadol is reported to be about the same as with Oxycodone and Morphine.

Like other opioids, Tapentadol has the potential to cause respiratory depression. All the usual precautions observed with the use of other opioids apply to this drug.

In addition there is the potential for abuse, misuse, or diversion that is associated with other opioid drugs. For these reasons, as well as the DEA's current strong bias towards very strict regulation of opioids, the DEA has designated Tapentadol as a schedule II.

It is currently available in 50mg, 75mg, and 100mg immediate release tablets which are dosed every 4 to 6 hours. There is no long-acting or sustained release dosage-form available, nor is there a liquid form available at this time. The approximate cost of a 15 day supply to the hospice for the median 75mg strength would be \$135.00 at this time (assuming an average usage of 75mg QID over the 15 day period).

The exact role of this new analgesic in hospice has not been clearly defined. It may have distinct advantages for patients suffering from moderate to severe neuropathic pain that have not responded to more traditional drugs or those who cannot tolerate existing medications due side effects or allergies. Tapentadol's dual mechanism of action is very similar to Tramadol, however, it appears that Tapentadol is more potent. Ideally this new drug would provide clinicians with an analgesic that has a potency level between Tramadol and Morphine with less side effects than morphine. Cost is another important consideration with any new drug. Tramadol and morphine, being generics, are just a small fraction of the cost of an equivalent dosage of Tapentadol (Nucynta). The schedule II classification also provides a barrier to more widespread utilization of this drug. Tramadol (Ultram) is not classified as a controlled substance. It will be interesting to see how effective and well tolerated this new analgesic with a dual mechanism of action turns out to be in clinical practice. Watch for ads on Nucynta soon.

FDA Announces Lantus Insulin-Cancer Link

FDA has announced that it is looking into studies that suggest an increased risk of cancer with Lantus Insulin (insulin glargine). Three of 4 observational studies reviewed by the FDA suggest an increased risk of cancer in patients using Lantus Insulin. Based on the currently available data, the FDA recommends that patients should not stop taking their insulin therapy without consulting a physician, since uncontrolled blood sugar levels can have both immediate and long-term serious adverse effects.



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Baclofen: Effective for Cancer Pain

A group of investigators from a Japanese palliative care unit recently published an article describing the benefits of Baclofen (Lioresal) for managing cancer pain.⁽¹⁾ This is significant since Baclofen, an effective muscle relaxant, has not previously been studied for its effect as an adjuvant medication specifically for managing cancer pain.

Baclofen has potent antispasmodic activity making it a logical choice for numerous conditions associated with muscle spasm and pain related to muscle spasm. There are also reports in the medical literature that describe the effectiveness of Baclofen for certain neuropathic pain syndromes such as trigeminal neuralgia as well as post herpetic neuralgia.⁽²⁾ Baclofen's mechanism for pain relief is thought to be mediated via the GABA receptors in the central nervous system, a mechanism distinctly separate from that of the opioids which are the primary category of drugs used to manage cancer pain.⁽³⁾ Adding Baclofen to opioid therapy may make sense from the perspective of attacking the pain from two separate mechanisms of action.

This study was limited to 25 cancer patients who had pain resulting from the following conditions: spinal metastasis, pelvic plexus invasion, thoracic wall invasion, neck invasion,

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bone metastasis, brachial plexus invasion, celiac plexus invasion, and thalamic pain.

The maintenance dosage range was 10mg-40mg per day in 2 to 4 divided doses. Pain was rated by the patient on a numerical rating scale (NRS) of 0 to 10. A 50% or greater reduction in pain according to the NRS was reported by 21 of the 25 patients after the addition of Baclofen. Side effects of sleepiness and GI symptoms were minimized by initiating therapy at a low initial dose of 10mg/day and titrating up to 40mg/day with gradual increases every 2 days depending upon response. Weakness is also a common side effect related to the muscle relaxant properties of Baclofen, however, in this study weakness was only noted in 1 patient. Baclofen was continued for a median duration of 114 days in the 21 patients who reported positive effectiveness.

The effectiveness of Baclofen in a few of the cancerous conditions is not too surprising since these conditions were likely to have a significant neuropathic pain component (ex; pelvic plexus invasion or spinal mets). The interesting finding is that it was also effective for other pain types such as bone metastases. This study suggests that Baclofen can be an effective adjuvant analgesic for managing cancer pain in combination with opioid therapy.

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FDA Reviews Acetaminophen and Liver Toxicity

An FDA advisory committee has recommended that the FDA consider withdrawing *all* combination products that contain acetaminophen to reduce the incidence of unintentional acetaminophen over- dosage and subsequent liver failure. This would include the withdrawal of Vicodin, Lortab, Norco, Percocet, Ultracet, Darvocet, Tylenol with Codeine and others. This move would essentially eliminate "Step 2" on the World Health Organization's three-step pain ladder, forcing analgesic therapy to be escalated from plain acetaminophen or an NSAID directly to Morphine or another similar strong opioid in one giant step. This may not be appropriate for many patients.

Considering the massive disruption in patient care that would result from actually withdrawing all of these combination products, it seems more plausible that the FDA may restrict acetaminophen content in these products to a maximum of 325mg per unit. Currently there are some combination products that contain 500mg-750mg of acetaminophen per tablet (Vicodin, Vicodin ES). The FDA is also considering lowering the maximum recommended total daily dosage of Acetaminophen from 4000mg to 3250mg.