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Oseltamavir for Flu in Children Younger Than 1 Year

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Tamiflu® (oseltamavir) is an antiviral agent that is indicated for prophylaxis of influenza and treatment of acute illness caused by influenza A or B viral infection with symptom onset within 48 hours. As of December 21, 2012 the FDA has expanded the indication of Tamiflu for treatment of influenza infection to include pediatric patients of ages 2 weeks to 1 year. When the product was originally approved in 1999, it was not indicated for the treatment of children less than 1 year of age, and it is still not indicated for influenza prophylaxis in children less than 1 year of age. The decision to expand the indication was based on data extrapolated from previous studies done in adults and children and two additional, safety and pharmacokinetic studies. [1-3]

Two open label trials evaluated the safety and pharmacokinetics of oseltamivir and oseltamivir carboxylate in influenza infected pediatric patients 2 weeks to less than 1 year of age (including premature infants at least 36 weeks post conceptional age). Subjects received oseltamavir at doses ranging from 2 to 3.5 mg/kg twice daily for 5 days depending on subject age. These clinical trials were not designed to evaluate clinical efficacy or virologic response. The trials provided adequate safety data to support the recommended dose selection for the treatment of acute illness in children 2 weeks to 1 year of age of 3 mg/kg twice daily.[2-3]

Of the 136 subjects under the age of 1 year enrolled and dosed in the trials, the majority of the subjects were male (55%), white (79%), non-Hispanic (74%), full term (76%) and infected with influenza A (80%). Pharmacokinetic data indicated that a dose of 3 mg/kg twice daily in pediatric subjects 2 weeks to less than 1 year of age provided oseltamavir concentrations similar to or higher than those observed in older pediatric subjects and adults receiving the approved dose and, by extrapolation to earlier study results, the FDA has concluded that is expected to provide similar efficacy. [2-3]

Current dosing recommendation for the treatment of flu in adults and children older than 2 years of age or those with body weight >40 kg is 75 mg twice daily for 5 days. The treatment dosing recommendation for oseltamivir for children aged ≥1 year who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg twice a day. For children less than 1 year of age, dosing is weight based at 3 mg/kg twice daily.[4]

In conclusion, Tamiflu is indicated for the treatment of flu in children as young as 2 weeks old when time since symptom onset is less than 48 hours. However, it has not been approved for prophylaxis of flu in children less than one year old. Children under the age of 2 years are among those in the highest risk category for developing complications related to influenza infection. As of January 5 2013, The Center for Disease Control (CDC) reports the death of 20 pediatric patients from this season's flu outbreak.[5] This new expanded indication of oseltamivir can become an important part of preventing deaths of pediatric patients.

<Click Here for References>

Eliquis Approved for Patients with Non-Valvular Atrial Fibrillation

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On December 28th, 2012 the FDA announced the approval of Eliquis (apixaban), an oral Factor Xa inhibitor, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation[1]. The approval of Eliquis was based on two pivotal clinical trials, the ARISTOTLE and AVERROES trials.

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study was a randomized, double-blind, head-to-head, non-inferiority trial of apixaban 5 mg twice daily versus warfarin (target INR 2.0-3.0) conducted in 18,201 patients[2]. Results of the study established that apixaban was not inferior to warfarin in the reduction of hemorrhagic stroke. Key secondary outcomes of the trial showed apixaban superior to warfarin in preventing stroke or systemic embolism.[2]

The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial was a randomized, double-blind study of 5,599 patients with atrial fibrillation who had increased risk for stroke and were unsuitable for vitamin K antagonist therapy.[3] Patients were randomized to either apixaban 5 mg twice daily or aspirin 81 to 324 mg daily. The primary outcome was the occurrence of stroke or systemic embolism[3]. Results of the trial showed apixaban reduced the risk of stroke or systemic embolism compared to aspirin (51 and 113; P<0.001) and had similar occurrence of major bleeding events (44 and 39; P=0.57).[3]

The recommended dose of apixaban is 5mg twice daily, or 2.5 mg twice daily in patients with at least two of the following: ≥80 years of age, ≤60 kg, or SCr ≥1.5 mg/dL.[4] Apixaban is metabolized mainly by CYP3A4 and is a substrate of P-glycoprotein (P-gp), therefore the dose should be reduced to 2.5 mg or avoided with strong dual inhibitors of CYP3A4 and P-gp and avoided completely with strong inducers of CYP3A4 and P-gp. The major adverse effect is the increased risk of bleeding. Similar to other factor Xa inhibitors, apixaban does not require monitoring of INR and there is no reversal agent available for the anti-coagulant effect.

Apixaban offers an alternative to other oral anticoagulants in the treatment of atrial fibrillation, such as warfarin, dabigatran, and rivaroxaban. Clinicians should use care in selecting appropriate therapy based on patient specific factors and be mindful of apixaban's potential for drug-drug interactions.

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Potential Drug Interaction: The Truth about NSAIDs and ACE Inhibitors

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The concomitant use of NSAIDs and ACE inhibitor (ACEI) has been associated with reducing the anti-hypertensive effects of the ACEI, as well as carrying the potential to inflict acute renal damage. The presumed mechanism of these effects on the kidneys and blood pressure stem from NSAIDs affect on prostaglandins (PG). These effects are typically not seen in normotensive patients or those with normal renal function, but occur more in patients with kidney or blood pressure pathologies.

Traditional NSAIDs target COX-1 and COX-2 for inhibition, while newer, more selective NSAIDs target just COX-2. COX-2 produces PG, which help regulate homeostasis within the kidneys. PGE2 is a tubular PG in the kidneys, where it regulates sodium, chloride, and water transport as well as renal medullary blood flow.[1] PGI2 is typically more in the vasculature. The arterioles, tubules, medullary interstitial cells, and mesangial cells of the kidneys produce both PGE2 and PGI2. Because of NSAIDs COX-2 inhibition, both new and older NSAIDs have potential for causing renal adverse effects. These adverse affects, depending on the patient, can include sodium and potassium retention, reductions in GFR, urinary sodium excretion, urinary PGE2, and 6-keto-PGF1α excretion, especially in the elderly of renally insufficient.[2,3] In patients with hypertension, COX-2 inhibition may cause worsening of hypertension and edema.[1]

Clinically, there is study-derived data demonstrating the relationship between NSAIDs, ACE inhibitors and these cardiovascular effects. Several of these studies are described below. It is important to note that some of these studies looked at multiple NSAIDs interacting with multiple anti-hypertensive medications, but for the purpose of this article, the focus will be on NSAIDs and ACE inhibitors.

In a study by MacDonald, et al., a comparison of lumiracoxib 100 mg once daily and ibuprofen 600 mg three times daily showed both agents caused changes in mean systemic ambulatory blood pressure (MSABP) in patients receiving concomitant blood pressure medications. For patients taking ACEI mono-therapy, lumiracoxib resulted in a fall of MSABP by 4.6 mmHg and ibuprofen showed an increase 3.7 mmHg. This was following 4 weeks of treatment with NSAIDs. This might suggest treatment with more selective NSAIDs may be beneficial in terms of blood pressure control.[4]

A cohort study of 1,204 subjects was conducted to investigate the systolic blood pressure effect of NSAIDs in patients taking various anti-hypertensive therapies. New anti-hypertensive therapy patients were identified using "The Anti-hypertensive Drug Database," and were compared as either "User" receiving "NSAIDs other than low-dose aspirin and

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acetaminophen" or a "Non-user," who were not. In the group taking ACEIs, the adjusted difference in systolic blood pressure reduction was 3.85 mmHg (95% CI: 1.16, 6.55) between "User" and "Non-user," with "User" having a lesser reduction.[5]

A prospective trial looked at 88 hypertensive patients being treated with lisinopril/hydrochlorothiazide and amlodipine to see the blood pressure effect of concomitant use of ibuprofen, acetaminophen, or piroxicam over a 3-month period. With lisinopril/hydrochlorothiazide, there was a SBP increase of 7.7-9.9% ($p<0.001$) when ibuprofen and piroxicam was also used.[6]

A 7-day, randomized, parallel group study conducted by Rossat et al compared 40 salt-depleted men taking celecoxib 200 or 400 mg twice daily, naproxen 500 mg twice daily, or placebo. Celecoxib showed short-term transient decreases in GFR and renal blood flow on day 1 with the 400 mg BID dose. Celecoxib and naproxen both decreased UO, sodium, lithium, and potassium excretion, as well as decreased water excretion.[7]

In a report by Dixit et al, 15 inpatients (mean 15.2 ± 2.3 years old) were found to have NSAID-induced acute kidney injury from taking the reportedly recommended doses. Of the 15, only one patient had pre-existing renal diseases. From the AKI, the patients experienced one of more of the following: proteinuria, hematuria, elevations in serum creatinine (mean 4.09 ± 4.24 mg/dL), and a mean eGFR 8.2 ± 20.5 mL/min.[8]

However, this drug-drug interaction is not entirely one-sided. ACE inhibitors are also implicated in acute kidney injury and a potential cause of acute renal failure (ARF). Wynckel et al. found ACE inhibitors could cause ARF in many patients without renal artery stenosis, typically who were volume depleted, and accounted for 9% of all acute kidney injury requiring hospitalization. These acute effects were especially prominent in CHF and the elderly.[9]

While there is evidence suggesting NSAID's potential to increase blood pressures of both hypertensive and normotensive patients, pain is also implicated in this issue. Pain causes a variety of stresses on the body, resulting in increased sympathetic activity and vascular resistance, heart rate, and consequently, blood pressure. Important things such as quality of life and sleep patterns are also affected by pain, which can be detrimental to a patient's overall health outcome, especial in terms of acute care.[10] This is important in weighing the risk vs. benefit of using NSAIDs for pain control. While there are other options for the management of pain (ie. acetaminophen, tramadol, opioid analgesics), some of these options carry their own adverse effects to be avoided (ie. addiction, tolerance, liver toxicity, CNS effects).

So who should be receiving combination NSAID and ACE inhibitor therapy? The above studies suggest that combination therapy has the potential to elevate blood pressure, with perhaps COX-2 selective agents having less of this effect. There is also evidence of acute kidney injury in both NSAID and ACE inhibitor. Patients at higher risk for elevation in blood pressure from NSAID use are those with pre-existing hypertension, while those at higher risk for renal adverse effects from NSAIDs include having liver dysfunction, renal dysfunction, CKD, salt depletion, hypovolemia, CHF, nephrotic syndrome, and those with pronounced proteinuria.[1] Recommendations for this combination of therapy are as follows:

For controlled hypertensive patients with healthy renal function, the combined use of NSAIDs and ACE inhibitors can be recommended. If combination therapy is needed in patients with impaired renal function and/or in those with less-controlled hypertension, therapy can still be recommended, however, regular monitoring of serum creatinine, GFR, and blood pressure will be warranted under those circumstances. If negative changes in renal or BP parameters are seen after administration of NSAID therapy, discontinuation of the NSAIDs should be considered to see if the values normalize, then alternative therapies to NSAIDs should be considered.

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