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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals, April 2009

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Update

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Evaluation of Intravenous Levetiracetam Use in Adult and Pediatric Patients: *Medication Use Evaluation*

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Levetiracetam (Keppra®) is an antiepileptic drug (AED) indicated in oral formulation as adjunctive therapy for myoclonic seizures in patients 12 years of age and older, partial seizures in patients 4 years of age and older, and primary generalized tonic-clonic seizures in patients 6 years of age and older.[1,2] Levetiracetam is an effective alternative to the traditional AEDs, which are known to be sedating and metabolized through the liver by the cytochrome P450 enzyme system. Levetiracetam is not metabolized by the liver, has low protein binding, and is excreted by the kidneys with few drug-drug interactions. The intravenous (IV) formulation of levetiracetam is only approved for adjunct therapy of partial-onset seizures in adults (≥16 years of age) when oral administration of levetiracetam is temporarily not feasible.[1,2] There is no FDA-approved indication for the use of IV levetiracetam in children, and the safety and efficacy of levetiracetam injections have not been established in patients less than 16 years of age.[3-5] Regardless of several case reports of the use of IV levetiracetam in the pediatric population, data on the dosing, safety, and efficacy in this population are generally lacking.[3-5] The IV formulation of levetiracetam has been found to be bioequivalent to the oral formulation, and appears to be well-tolerated in healthy adult patients even at fast infusion rates.[1,2,6] In addition, a recent study by Goraya and colleagues suggests that IV levetiracetam may also be safe and effective in children with a variety of seizure disorders.[4]

IV levetiracetam has been used off-label in conditions such as status epilepticus, seizure prophylaxis in traumatic brain injury, migraine prophylaxis, and manic bipolar I disorder.[7,8] Even though there is some evidence for use in these indications, current literature lacks large prospective trials evaluating the safety and efficacy of IV levetiracetam in these patient populations.[7,8] At the Medi-

cal University of South Carolina (MUSC), IV levetiracetam is seemingly used in both adult and pediatric patients for indications in which there is limited supporting evidence and at unsupported doses. In addition, it appears that IV levetiracetam is also used in patients who are able to tolerate oral medications. The purpose of this medication use evaluation was to assess utilization of IV levetiracetam in both adult and pediatric patients.

METHODS

A retrospective chart review was conducted from November 2006 to October 2008 including adult and pediatric patients receiving IV levetiracetam during hospitalization. Patients were identified using the Clinical Resource Manager database available through a search of the University Health System Consortium (UHC). Charts were reviewed using the OACIS Clinical Care Suite database. To be eligible for inclusion in this study, patients had to have at least 1 documented order for IV levetiracetam. Patients were excluded if they were pregnant at the time of levetiracetam administration.

The primary outcome was to determine the potential cost-savings resulting from appropriately switching from IV to oral levetiracetam in patients able to tolerate oral therapy.

Secondary outcomes include assessing dosing among pediatric and adult patients and appropriateness of use by indication as determined by the FDA in the adult population.

Data collection included patient demographics and dose, duration, and indication of levetiracetam therapy. Diet was documented by indicating whether the patient was receiving nothing by mouth (NPO), enteral nutrition, or an oral diet. Concomitant anti-epileptic medications were also recorded.

For the purpose of this review, using the IV route for levetiracetam administration was considered inappropriate in patients taking other medications orally. Indication was determined by thoroughly searching patients' electronic charts for documentation. This MUE was approved by the MUSC Institutional Review Board. Data collection and analysis were performed using a Microsoft Excel™ spreadsheet.

DATA ANALYSIS

Patient Demographics

From a database of over 1200 patients, a total of 552 patients were randomly identified and included in the data analysis. Of the 552 patients, 419 were adult patients and 133 were pediatric patients. For the purpose of this study, these 2 populations were analyzed separately. In the adult and pediatric populations, the average age was 54 years and 10 years, respectively. The majority of the adult and pediatric patients were Caucasian, with African Americans being the second largest population represented (Table 1). No other significant demographic differences were noted among patients.

During the time when these patients received IV levetiracetam, only 34.9% of the adult population and 18.8% of the pediatric population had a nutritional status classified as NPO. The remaining patients were receiving nutrition either enterally or orally. Additionally, 59.7% of adult patients were receiving concomitant oral medications, while only 15% of pediatric patients receiving IV levetiracetam were receiving other oral medications (Table 2).

Indications for Use

Seizure prophylaxis (50.1%) was the most commonly cited indication for use of IV levetiracetam in the adult population followed by generalized seizure (22.7%).

Table 1: Patient Demographics

Characteristic	Adults	Pediatrics
Gender		
Male	217 (51.8%)	78 (58.6%)
Female	201 (48.0%)	55 (41.4%)
Not Specified	1 (0.2%)	0 (0.0%)
Race		
Caucasian	233 (55.6%)	66 (49.6%)
African American	167 (39.9%)	59 (44.4%)
Hispanic	10 (2.4%)	8 (6.0%)
Other	9 (2.1%)	0 (0.0%)
Age (years)		
Average	54	10
Range	18-100	0-19

Table 2: Oral Status

Characteristic	Adults	Pediatrics
Nutrition		
NPO	146 (34.9%)	25 (18.8%)
Enteral	123 (29.3%)	18 (13.5%)
Oral	150 (35.8%)	89 (66.9%)
Not documented	0 (0.0%)	1 (0.8%)
Concurrent oral medications		
Yes	250 (59.7%)	20 (15.0%)
No	169 (40.3%)	112 (84.2%)
Not documented	0 (0.0%)	1(0.8%)

Generalized seizure (60.2%) was the most commonly cited indication for use of IV levetiracetam in the pediatric population followed by seizure prophylaxis (13.5%) (Table 3). IV levetiracetam was used as monotherapy in 66% of adult patients and in 56% of pediatric patients. Dosing patterns in the adult and pediatric patient populations are shown in Table 4.

In the adult population, neurology or neurosurgery prescribed IV levetiracetam 63% of the time and were consulted for 14.6% of the other doses prescribed (Figure 1). Among pediatric patients, neurosurgery was the primary service in only 3% of patients; however, neurology or neurosurgery were consulted for 92.5% of IV levetiracetam doses prescribed (Figure 2).

RESULTS SUMMARY

The majority of adult patients, and nearly 20% of pediatric patients in this review receiving IV levetiracetam were receiving concomitant oral medications. The IV formulation of levetiracetam is significantly more expensive than the oral formulation; therefore appropriately switching patients to oral therapy can provide a cost savings to the organization. A cost analysis of converting from IV to oral levetiracetam demonstrated a potential cost savings of $37,100 over the selected time frame in this population. This figure was based on cost of the 500 mg oral and IV formulations. Since the doses analyzed only represented about one-third of the total administered doses in the timeframe analyzed, one could presume the potential cost-savings could be even more substantial.

Secondly, in the analysis of the patterns of IV levetiracetam use, it was discovered that nearly 97% of the time IV levetiracetam was used for a non-FDA approved indication, most commonly seizure

Table 3: IV Levetiracetam Indication

Seizure Type	Adults	Pediatrics
Generalized	95 (22.7%)	80 (60.2%)
Myoclonic	7 (1.7%)	2 (1.5%)
Partial	11 (2.6%)	16 (12.0%)
Prophylaxis	210 (50.1%)	18 (13.5%)
Status epilepticus	21 (5.0%)	16 (12.0%)
Not specified	75 (17.9%)	1 (0.8%)

Table 4. Dosing Patterns

	Adults	Pediatrics
Mode	1000 mg, twice daily	10 mg/kg/dose, twice daily
Median	1785 mg, daily	15.3 mg/kg/dose
Range	500 mg - 4000 mg, daily	2.4-50 mg/kg/dose, twice daily

Figure 1: Prescribing Patterns in the Adult Population by Service

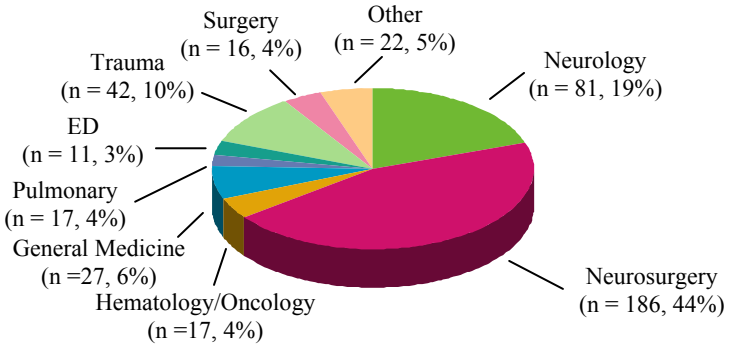
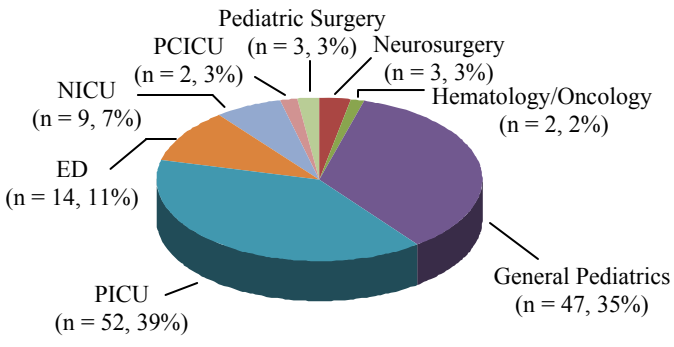


Figure 2: Prescribing Patterns in the Pediatric Population by Service



prophylaxis in adults. Furthermore, despite no approved indication for its use in children, it was still frequently used. In conclusion, based solely on patients' ability to tolerate oral medications, IV levetiracetam was inappropriately prescribed in approximately 60% of the adult population and in 15% of the pediatric population evaluated. Based on the potential cost-savings identified in this evaluation, a method should be implemented to identify appropriate candidates for conversion to oral or alternative therapy.

LIMITATIONS

- Retrospective chart review was dependent on reliable documentation
- Some patients were taking oral medications despite documented NPO orders
- Oral medications on medication administration record not necessarily indicative of administration
- A small number of patients over the age of 16 years were included in the pediatric data analysis because they were covered by pediatric services
- Some patients received an IV loading dose of levetiracetam but were subsequently converted to oral therapy

CORRECTIVE ACTIONS

The following actions have been approved by the Pharmacy and Therapeutics Committee:

- Educate on indication for levetiracetam use as well as oral versus IV use
  - If a patient is being administered other oral or enteral medications, oral (enteral) levetiracetam should be considered.
  - The cost of oral levetiracetam is less expensive than IV levetiracetam.
- Collaborate with neurology and clinical pharmacy services to develop an IV to PO conversion program for levetiracetam.

Did You Know… Health Advisory for Swine Influenza

Swine influenza is a respiratory disease of pigs caused by type A influenza that regularly cause outbreaks of influenza among pigs. Swine influenza viruses do not normally infect humans; however, human infections do occur, and cases of human-to-human spread has been documented. Only 12 human infections with swine influenza were reported from 10 states in the United States since December 2005. However, a number of confirmed human cases of a new strain of swine influenza A (H1N1) virus infection have been identified since March 2009. The current outbreak areas include Mexico, Texas (2), California (7), Kansas (2), New York (8), and Ohio (1). A public health emergency has been called; however, a pandemic has not been declared.

Laboratory studies indicate susceptibility to neuraminidase inhibitors (oseltamivir, zanamivir) but resistance to the adamantanes (amantadine, rimantadine). It is not known whether the sensitivity of rapid tests for human influenza A:H1N1 will be equivalent for swine influenza A:H1N1. Because the current cases are dispersed over a fairly wide geographic area, containment is not a feasible option, and attention is focusing on other tools to slow the spread of infection. There is currently no vaccine available and it is unknown whether this season's vaccine provides any protection. Seed virus has been collected for possible vaccine development.

Currently, the CDC is the source for identification of the virus in non-typable influenza A positive samples. As soon as we receive guidelines for diagnostic testing from the state we will share this information with you. With novel influenza viruses, the modes of transmission are not always immediately clear. Interim guidelines from the CDC for infection control include placing hospitalized patients with swine influenza into negative pressure isolation rooms on airborne, droplet and contact precautions. Staff participating in aerosol generating activities should wear a fit tested N95 mask. General precautions are listed in Table 1.

Table 1. General Preventative Guidelines for Swine Influenza

There are everyday actions people can take to stay healthy.
- Cover your nose and mouth with a tissue when you cough or sneeze.
- ***Wash your hands*** often with soap and water, especially after you cough or sneeze. Alcohol-based hands cleaners are also effective.
- Avoid touching your eyes, nose or mouth. Germs spread that way.

Try to avoid close contact with sick people.
- Influenza is thought to spread mainly person-to-person through coughing or sneezing of infected people.
- If you get sick, CDC recommends that you stay home from work or school and limit contact with others to keep from infecting them.

FORMULARY UPDATE FOR MARCH 2009

In March 2009, the Pharmacy and Therapeutics Committee approved the actions listed below. The formulary effective date was April 15, 2009.

ADDITIONS

Gadoteridol (ProHance®) is a gadolinium-based, nonionic contrast medium for magnetic resonance imaging (MRI). It has an improved safety profile for those patients at risk of developing nephrogenic systemic fibrosis (NSF). Therefore, prescribing will be restricted to the following patients:
- Chronic kidney disease stage 3, 4, or 5
- Acute kidney injury
- Renal or liver transplant
- End-stage renal disease that requires MRI with gadolinium or a magnetic resonance angiogram (MRA) for a life-threatening case without an alternative imaging study

Single-dose vials: 279.3 mg/mL

Dexrazoxane (Totect®) is the only FDA-approved agent for extravasation injury following IV anthracycline administration. It is an iron chelator that may prevent iron-mediated free radical production and is a reversible topoisomerase II inhibitor. It is injected in 3 serial doses and is supplied in a kit for easier administration. Since it is rarely used and expires within 2 years, the manufacturer of the kit includes a replacement policy for up to 6 years. Dexrazoxane comes in a brand (Zinecard®) and generic IV form, but there would be issues with reimbursement for using the non-approved IV formulation for extravasation injury in the outpatient setting. The Totect® kit will be available from the Hollings Cancer Center Pharmacy.

Solution for injection: Totect® injection kit

RESTRICTION ADDITION

Iopromide (Ultravist®) will be restricted to use only in cardiac computer tomography (CT) scans. This restriction will help assure appropriate market share with the contracts for iohexol (Omnipaque®) and iodixanol (Visipaque®).

370-mg I/mL vials

LINE EXTENSIONS

- Vancomycin 50 mg/mL extemporaneous oral solution
- Oseltamivir (Tamiflu®) 30- and 45-mg capsules; 12-mg/mL suspension
- Fluoxetine 10-mg tablets
- Aripiprazole (Abilify®) 2-mg tablets
- Beclomethasone 1-mg/mL extemporaneous oral suspension (in corn oil)
- Supersaturated calcium phosphate (Caphosol®) mouth rinse

DELETIONS

- Gadopentetate dimeglumine (Magnevist®)
- Iopromide (Ultravist®) 300-mg I/mL
- Iopamidol (Isovue®-370)
- Neutra-Phos®-K powder
- Vancomycin 16.67 mg/mL extemporaneous oral solution
- Fluoxetine 10-mg capsules *(when supplies are depleted)*
- Fleet® Phospho-Soda solution
- Lanolin breast cream (Lansinoh®)
- Enalaprilat 2-mL vial *(1-mL vial will be available)*

CHARTS, GUIDELINES, AND ORDER FORMS

The list of Chemotherapy and Hazardous Medications has been updated to reflect new medications that require special handling and storage. It can be found as part of Appendix 1 to the Handling and Disposal of Hazardous Drugs (Policy C155).

The Pediatric Mayday Card has been updated to reflect the PALS guidelines and the MUSC Continuous Infusion Guidelines. These cards will be found in the pediatric emergency tackle boxes.