UFHealth
SHANDS HOSPITAL

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Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 21, 2014. 1 drug was added in the *Formulary*, 1 drug was designated nonformulary and not available and 1 drug and 1 drug class had criteria for use changes.

◆ ADDED

Cisatracurium besylate (Nimbex®)*

**Restricted to utilization in patients with diagnosed Acute Respiratory Distress Syndrome (ARDS)*

◆ NON-FORMULARY AND NOT AVAILABLE

Luliconazole (Luzu®)^

^Patient may use their own

◆ CRITERIA FOR USE CHANGES

Dexmedetomidine (Precedex®)*

**Criteria expanded to include use in patients experiencing alcohol withdrawal symptoms with refractory response to conventional agents.*

Fluoroquinolone Class Criteria for Use Changes

◆ DELETED

None

◆ HIGH-PRIORITY NON-FORMULARY

None

◆ THERAPEUTIC INTERCHANGES

None

Cisatracurium besylate (Nimbex®) was requested for *Formulary* addition by the Department of Surgery for use in patients with diagnosed Acute Respiratory Distress Syndrome (ARDS) as well as in patients at risk for Compartment Syndrome. These two uses were considered separately by the

(continued on next page)

MEDICATION SAFETY

Insulin Pen vs. Insulin Vial Use: Balancing the Risks

In February 2013, the Institute for Safe Medication Practices (ISMP) issued a Medication Safety Alert detailing ongoing concerns with insulin pen use in the inpatient setting.[1] This bulletin addressed the potential for reuse of insulin pens on multiple patients, which carries the risk of blood-borne pathogen exposure. In this alert, the ISMP advised institutions to evaluate their current practices and to strongly consider the discontinuation of insulin pen use in the hospital setting.

The above alert was published after reports of potential exposure to human immunodeficiency virus (HIV), hepatitis B, or hepatitis C in 700 patients at a New York hospital secondary to reuse of insulin pens (same insulin pen, but different insulin needle).[2] That same week, an addition potential exposure to 1915 patients in another New York based institution was described.[2] It is important to note that neither of these reports yielded documented transmission of blood-borne pathogens however one patient is known to have brought suit for a potential Hepatitis C infection. These exposures came on the heels of a large potential exposure at a VA hospital in Texas which was described in 2009.[3]

With the growing concern for potential pathogen exposure, a multidisciplinary task force was created at UF Health Shands Hospital to evaluate current practice with regards to insulin pen utilization. The aim was to evaluate current risk of pathogen exposure compared to risk of medication errors associated with conversion from insulin pens to insulin vials.

A survey was conducted via the University Health Systems Consortium (UHC) list serve in March of 2013. Of the 64 respondents (~55% response rate), 61% of institutions utilize only insulin vials, 31% utilize a combination of insulin pens at vials, and 8% use insulin pens exclusively. At the time of the survey, UF Health Shands Hospital was using a combination of pens and vials.

A literature evaluation was performed to evaluate the risk of biological contamination with insulin pen usage. The results of the literature evaluation are outlined in the table below.

Pub. Year	Authors	Study Site	# of Pens	Rate of Pen Cartridge Contamination
1998	Le Floch et al	France	120	Microscopic Exam: 58% Hemoglobin Assay: NA
2001	Sonoki et al	Japan	146	Microscopic Exam: NA Hemoglobin Assay: 4.1%
2013	Herdman et al	United States	125	Microscopic Exam: 4.8% Hemoglobin Assay: 0.8%

*Table references: Le Floch[4], Sonoki[5], Herdman[6]

In 2012, Hakre and colleagues analyzed actual disease rates in patients after a described exposure who were at risk of disease transmission at William Beaumont Army Medical Center.[7] Of the 2,113 patients prescribed insulin pens during the previously described "at risk" period, 71% underwent testing for HIV and Hepatitis B and C. Six (0.4%), 6 (0.4%), and 56 (3.7%) were positive for these diseases respectively. The authors concluded that transmission could not be excluded but evidence did not point to a large outbreak. This conclusion was based on: lack of evidence of acute disease after potential exposure to shared insulin pens, sequencing of virus from patient samples did not indicate a close relation, and the high prevalence of pre-existing infection in this population (>50%). Of note, 74% of nurses in this study reported that they received training on insulin pen use, yet 24% believed that insulin pens were being reused on more than one patient.

A conversion from insulin pens to insulin vials may be associated with an increased risk of medication error.

(continued on page 4)

Formulary update, *from page 1*

Pharmacy and Therapeutics Committee. Cisatracurium was previously removed from the *Formulary* in 2002 with atracurium selected as the favored *Formulary* agent.

Cisatracurium is an intermediate acting neuromuscular blocking agent that is 1 of 10 isomers of atracurium. It produces skeletal muscle relaxation after intravenous administration and is indicated for tracheal intubation as adjunct to general anesthesia and as a skeletal muscle relaxant during surgery or mechanical ventilation. Cisatracurium undergoes organ-independent Hofmann elimination to form inactive metabolites, a potentially desirable metabolic pathway for patients in need of skeletal muscle relaxation who have renal dysfunction.

At the time of evaluation, cisatracurium was designated non-formulary and not available with atracurium available for use both in the ICU and operative setting. Cisatracurium has been postulated to have a decrease in adverse reactions secondary to a decrease in laudanosine concentrations which has been associated with many of the toxicities of atracurium. In addition, cisatracurium is proposed to have a decreased histamine release which would lessen the risk of hypotension in exposed patients.

ARDS – Two trials have evaluated the use of cisatracurium for the treatment of ARDS. The first was a small trial consisting of 36 patients who received either bolus followed by continuous infusion cisatracurium or placebo. After 48 hours of therapy, patients receiving cisatracurium were noted to have statistically significant decreases in inflammatory markers including IL-1β, IL-6 and IL-8. These patients also had a significant sustained improvement in the PaO_2:FiO_2 ratio throughout the 5 day study.

A larger study investigating bolus and continuous infusion cisatracurium versus placebo was conducted in 340 patients with ARDS. Patients had a decreased hazard ratio for death in the treatment group vs. control at 90 days. No difference in 28 day mortality was noted. Patients with cisatracurium therapy were also noted to have significantly more ventilator-free days than the placebo counterparts.

Based upon these data, the P&T Committee elected to add cisatracurium in the *Formulary* restricted to patients requiring mechanical ventilation with ARDS as part of a defined ARDS protocol.

COMPARTMENT SYNDROME – One abstract has been published describing the use of cisatracurium in 10 patients for the prevention of abdominal compartment syndrome in patients with intra-abdominal hypertension (IAH). Patients received a single bolus dose of cisatracurium and were noted to have a decrease in intra-abdominal pressure from 18mmHg to 14mmHg at 15 minutes. Patients returned to baseline abdominal pressures within 2 hours in the absence of repeated doses being administered. Based on these data, the International Conference Experts on Intra-Abdominal Hypertension and Compartment Syndrome made a 2C recommendation to consider a brief trial of neuromuscular blocking agents in patients with mild to moderate IAH in conjunction with other efforts to decrease abdominal pressures. No suggestion of a preferred agent was indicated.

Based upon these limited data, the P&T Committee recommended against the use of cisatracurium for the prevention of Compartment Syndrome.

Luliconazole (Luzu®) is a topical azole antifungal cream indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum* or *Epidermophyton floccosum* in patients 18 years of age or older.

The Committee recommended that this agent be designated Non-Formulary and Not Available with patients able to use their own medication as approved in the Patient's Own Medication policy. This recommendation was verified with the Anti-Infective Subcommittee.

Dexmedetomidine (Precedex®) has been reviewed by the Pharmacy and Therapeutics (P&T) Committee in 2002, 2004, 2008, and for use in pediatrics in 2010. The Committee voted to designate dexmedetomidine Non-Formulary and Not Available in 2002 and 2004 based on unimpressive results presented in clinical trials. The literature at the time of review failed to sufficiently demonstrate superiority of dexmedetomidine to midazolam or propofol, despite costing 28 and 10 times more than the comparator agents, respectively.

Dexmedetomidine was added in the *Formulary* with restrictions in 2008 based on new evidence for use in awake craniotomy, awake intubation, ventriculostomy placement for non-intubated patients, and transition to extubation for agitated patients who are difficult to wean from the ventilator. Use was limited to 24 hours for these indications. In 2010, dexmedetomidine was approved for use in pediatrics with restrictions outlined in the Pediatric Dexmedetomidine Order Set. A medication-use evaluation in 2009 revealed modest use of the product at UF Health Shands Hospital, with an average of 8 administrations per month primarily for awake intubation. In 2012, dexmedetomidine was evaluated for four possible criteria additions: opioid sparing effects in hospitalized non-OR patients, opioid sparing effects in operative settings, opioid sparing effects in post-surgical patients and primary analgesia in OR patients on buprenorphine where opioids are contraindicated or less effective. The Committee approved use in the OR for patients who were not responding to opioids or who were receiving buprenorphine.

At present, dexmedetomidine was requested for evaluation by the Department of Surgery for expansion of current criteria to include use in patients experiencing alcohol withdrawal to avoid intubation and for use beyond 24 hours to transition patients to extubation. These two indications were considered separately by the Committee.

ALCOHOL WITHDRAWAL – Several case reports have been published describing the use of dexmedetomidine for the treatment of withdrawal symptoms associated with cocaine, opioid, benzodiazepine, and alcohol in adult patients. The most common regimens include a loading dose followed by continuous infusion of 0.175 to 0.7 mcg/kg/hr. Duration of infusion varied from 36 hours to 7 days in these reports. To date, there have been no randomized, controlled trials evaluating the efficacy of dexmedetomidine to prevent intubation in patients experiencing withdrawal symptoms.

Individual case reports as well as case series have described the successful use of dexmedetomidine in treating patients with alcohol withdrawal symptoms. The majority of these retrospective evaluations detail decreases in benzodiazepine consumption, avoidance of mechanical ventilation, and decreased symptoms of agitation and withdrawal including tachycardia and systolic hypertension. Overall, these reports describe utilization of dexmedetomidine when other agents have failed.

Based upon these data, the P&T Committee recommended the expansion of current criteria to allow for use of dexmedetomidine to prevent mechanical ventilation in patients experiencing alcohol withdrawal. This expansion of criteria is contingent upon development, presentation, and approval of an alcohol withdrawal protocol by the Committee.

(continued on next page)

Formulary update, *from page 2*

TRANSITION TO EXTUBATION – To date, no prospective study has been conducted evaluating time to extubation as a true primary endpoint. One study did describe duration of mechanical ventilation as a co-primary endpoint; however, this study had significant limitations including differences in the levels of sedation and drug discontinuation rates between groups, as well as non-standardized practices for weaning and extubation. The studies described below evaluated extubation as a secondary endpoint.

In total, thirteen studies and one meta-analysis were included in the review of dexmedetomidine for transition to extubation. Ten of the 13 studies failed to show a significant difference in time to extubation or duration of intubation when comparing dexmedetomidine to either propofol or midazolam. One of the studies identifying a significant difference has already been discussed above. One study identified a significant difference in duration of intubation with a p value of 0.04. The actual difference in duration of intubation was 1 hour which is not clinically significant, even in the context of statistically significant findings. In the final study showing statistically significant differences in time to extubation, there was a 1.9 day difference between the dexmedetomidine and the midazolam group (p 0.01). This finding was confounded by the fact that patients in the midazolam group received significantly more fentanyl than the dexmedetomidine group which may have increased the level of sedation and thus increased the time to extubation.

Finally, a meta-analysis was published in December 2013 describing the use of dexmedetomidine versus propofol in adult intensive care unit patients. This analysis included 5 studies which evaluated ICU length of stay, duration of mechanical ventilation and ICU mortality. With respect to ICU length of stay, a statistically significant decrease in ICU length of stay was associated with receipt of dexmedetomidine. This decrease was 0.81 days and was driven solely by a single trial included in the evaluation. Removal of this study and re-evaluation failed to demonstrate a statistically significant difference. No difference was noted for duration of mechanical ventilation or ICU mortality.

Based upon these data, the Committee recommended against the expansion of the 24 hour restriction for use of dexmedetomidine.

Fluoroquinolone Criteria Changes were proposed by the Anti-Infective Subcommittee in response to additional safety alerts released by the FDA in late 2013. Following a review of the FDA Adverse Event Reporting System (AERS) database, permanent nerve damage associated with fluoroquinolone (FQ) use continues to be a problem. This is the second warning added to these package labels in the last 5 years. Coupling the safety concerns with eroding local susceptibility patterns, especially with *E. coli* and *P. aeruginosa*, the Anti-infective Subcommittee members reviewed the adverse event profile of this class of agents.

Upon review of the data, the following issues were identified:

- In the past 15 years, 4 FQ have been removed from the market due to severe adverse events: trovafloxacin (hepatitis), sparfloxacin (photosensitivity reactions and cardiotoxicity), grepafloxacin (cardiotoxicity), and gatifloxacin (dysglycemia). In addition, 2 other agents failed FDA approval due to concerns for adverse events observed in clinical trials.
- Discussion with Subcommittee members noted the new warning and previous warnings are class effects. Warnings reviewed with the group included: tendinopathy, neuropathy, central nervous system effects (including seizures), cardiotoxicity, dysglycemia, photosensitivity reactions, and hepatitis. Risk factors for these events are varied, but center on elderly (> 65) patients with kidney disease and other chronic comorbid conditions.
- Susceptibility for *E. coli* and *P. aeruginosa* to these agents has eroded at UF Health Shands Hospital. Resistance rates in 2013 are approximately 30% for *E. coli* and 20% for *P. aeruginosa*. Based on these data, FQ can no longer be considered as 1st line agents for the management of urinary tract infections, intra-abdominal infections, or as adjunctive therapy in patients with healthcare-associated infections.

Based on available information, committee members made the following recommendations to FQ criteria for use.

- Add levofloxacin to the "Restricted at 72 hours" category
- General recommendations for ciprofloxacin/levofloxacin
  - Restricted at 72 hours
- When empiric criteria are met, ciprofloxacin and levofloxacin will have an automatic stop date of 3 days. Continuation of therapy will require compliance with approved criteria.
- If ordered as empiric therapy for indications outside of approved criteria it will be restricted immediately and require approval from either the Antimicrobial Management Program or Infectious Diseases Consult.
  - Based on decreasing susceptibility amongst Enterobacteriaceae (*E. coli* resistance at 30%) and recommendations from clinical guidelines, FQ will not be approved as 1st line therapy for Urinary Tract and Intra-abdominal infections in patients without Type 1 immune mediated hypersensitivity reactions (i.e. penicillin-allergic patients).
  - Due to poor activity against Staphylococcal species, FQ will not be approved for empiric management of skin/skin structure infections in patients without Type 1 immune mediated hypersensitivity reactions.
- **Criteria recommendations**
  - Empiric treatment of health-care/hospital acquired infections (pending culture and sensitivity analysis) in patients with a documented severe allergy to β-lactam antibiotics.
  - Definitive therapy for a documented pathogen resistant to other narrower spectrum agents or in patients with severe allergy to β-lactam antibiotics.
  - Alternative to aminoglycoside when combination therapy is warranted
- Patients at risk for renal dysfunction (includes ICU and non-ICU patients) i.e. receipt of other nephrotoxic agents, pre-existing renal failure, s/p kidney transplant, and multi-organ failure.
- **Levofloxacin specific criteria**
  - Empiric treatment of community acquired pneumonia
  - Adjunctive therapy for management of atypical bacteria (e.g. Legionella)
  - Prophylactic therapy in bone marrow transplant recipients
- **Ciprofloxacin criteria**
  - Not indicated for the management of community acquired pneumonia

All changes to criteria were considered individually. In addition, the use of FQ therapy weekly for spontaneous bacterial peritonitis (SBP) prophylaxis was discussed. This was not assessed by the Anti-Infective Subcommittee and will be brought back for further discussion after evaluation of the data. In addition, it was noted that these changes would necessitate a prolonged roll-out period in order to educate all physicians, nursing, and pharmacy staff on changes to the criteria for use. The Committee will be notified when full implementation has occurred.

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Insulin,
from page 1

Just as insulin pen dosing is easier for patients it is also easier for nurses. Without a pen device, the nurse must prepare the insulin using an insulin syringe (no other type of syringe) and draw up the correct number of units / volume. Anecdotally insulin dosing errors appear to be lower with the use of insulin pen devices than vials. At UF Health Shands Hospital, insulin pens were instituted in 2006 with most insulin products dispensed as pen devices (with the exception of regular insulin). If pens were eliminated, the task force felt that there would be potential increases in insulin dosing errors.

Most ambulatory patients receiving insulin use insulin pens to administer their insulin due to convenience and ease of use mentioned above. Because of this, inpatient use of insulin pens facilitates patient diabetes education during a hospital stay. Knowledge of correct insulin administration technique is important for patients and families when working to maintain good glycemic control and insulin safety at home. In addition to concerns surrounding possible increases in insulin dosing errors in the hospital, removal of insulin pens from the inpatient setting would create a barrier for optimal diabetes education during hospitalization.

The upcoming implementation of barcode medication administration (BCMA) provides an opportunity for nurses to receive active alerts at the bedside if the wrong patient's insulin pen is selected for administration. Additionally BCMA wrong-patient alerts could provide real-time alerts to others, such as pharmacists or nurse managers of a wrong-patient insulin pen scan. Involving these team members could help further prevent cases of pen sharing. In combination with ongoing educational efforts, this added layer of safety will help further prevent cases of insulin pen sharing.

After careful consideration of the above factors, the task force has recommended the continued use of insulin pens at UF Health Shands Hospital. The risk of medication errors with insulin vials, combined with a less than optimal patient education environment if insulin pens are removed from the hospital was felt to outweigh the potential risk of a patient contracting a blood-borne pathogen due to pen sharing. Further, the planned implementation of BCMA will provide an added reliable layer of safety to prevent cases of insulin pen sharing. Therefore, UF Health Shands Hospital will continue to dispense insulin pens labeled for individual hospitalized patients. This decision was supported by hospital leadership.

The task force encourages staff to familiarize themselves with current policies and procedures surrounding this high-alert medication and will continue to evaluate current practices to ensure we are providing the safest care for our patients. Ongoing education will be provided for nurses on this important issue.

– Ji Lee, PharmD and Carrie Lagasse, PharmD, BCPS

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