UNIVERSITY HOSPITAL
Pharmacy News
UNIVERSITY HOSPITAL
Newark, New Jersey

Third Quarter 2013
Vol. X, Issue 3

Special Points of Interest:

- P&T Update-Formulary Addition/Deletion
- Policy and Procedures/ Floorstocks Update
- Welcome New Pharmacist

P&T Update

Formulary Addition/Deletion

1. Indomethacin (Indocin®) rectal suppository – formulary addition approved
   Indomethacin is a non-steroidal anti-inflammatory drug that is FDA approved for the management of rheumatologic and musculoskeletal conditions.
   Formulary addition – Approved
2. Epinephrine 0.3 mg/0.3mL (EpiPen®) – line extension
   Members reviewed a line extension request for EpiPen® (epinephrine 0.3 mg/0.3mL) syringes requested by the Ambulatory Care Center (ACC) for stock in the emergency kits. Approved for usage in the ACC emergency kits only.
3. Reteplase recombinant (Retavase®) – formulary deletion approved
   Motion was made to remove reteplase recombinant (Retavase®) from the hospital formulary based on its low usage and availability of alternative therapy (alteplase).
   Formulary deletion – Approved
4. Muromonab-CD3 (OKT3) – formulary deletion
   Manufacturer discontinued – formulary deletion approved
5. Lepirudin (Refludan®) – formulary deletion
   Manufacturer discontinued – formulary deletion approved
6. Lidocaine Ophthalmic gel 3.5% (Akten®) - formulary addition
   Akten® 3.5% is a local anesthetic indicated for ocular surface anesthesia during ophthalmological procedures. The current formulary alternatives are Lidocaine 2% jelly, Lidocaine 4% drops, Tetracaine, and Proparacaine. The price for Akten® 3.5% gel is $18.00 vs. $2-$4/unit for the formulary alternatives. – Formulary addition not deemed necessary at this time
7. Darunavir 800mg tablets – line extension
   Darunavir 400mg tablets are no longer available by the manufacturer. A motion for formulary addition of darunavir 800mg tablets was proposed. – Formulary addition of darunavir 800mg tablets, formulary deletion of darunavir 400mg tablets approved

Policies and Procedures/Floorstock Update

1. 831-200-057 Patient Care Event Reporting – ADR/ME
   Revisions to the Patient Care Event Reporting policy were presented for member review and approval. Definitions and descriptions of physical and chemical incompatibility were added as outlined by regulatory agencies. – Approved
2. 707-500-122 Automatic Therapeutic Exchange Policy Update
   The policy has been revised to reflect the new workflow due to implementation of EPIC CPOM. Providers/RPHs get pop up alerts in Epic at the data entry or medication verification screen to automatically substitute the product if they select a medication from the approved ATEP (automatic therapeutic exchange) list. Providers must indicate DO NOT EXCHANGE if there is a compelling therapeutic reason for not allowing this automatic substitution. – Approved
3. 707-300-101 Hospital Formulary Policy Update
   Formulary addition request form is updated to meet TJC standards for specifying doses of the requested product in special populations on the form. – Approved
4. 707-700-114 Epidural Analgesia Policy Update
   The expiration time for a PCEA order is extended to 72 hrs. from 24 hrs. The PCS group has made changes in the RN workflow for documentation on flow sheets, inspection of epidural site, and patient monitoring. – Approved
5. 2012 Antimicrobic susceptibility report (antibiograms) – Approved

Sirturo® (Bedaquiline): Novel TB Drug with Contradictory Findings

While not as common in the United States, tuberculosis is a big concern in several other countries including India, China, and Eastern Europe. This highly infectious illness has developed considerable resistance over the years; almost 50% of patients in countries such as Peru, Thailand, and Russia are resistant to at least one second-line therapy. Drug-resistant tuberculosis is associated with higher cost of treatment, longer duration of treatment, greater likelihood of treatment failure, and increased mortality.[1]

At the end of 2012, Sirturo® (bedaquiline) became the first tuberculosis drug with a novel mechanism of action to be approved by the FDA in 40 years. The FDA granted bedaquiline fast track approval, priority review, orphan drug status, and approved the drug for combination treatment for multi-drug resistant (MDR) pulmonary tuberculosis when other treatments are not available.[1] MDR tuberculosis is tuberculosis that is resistant to two common first-line therapies: isoniazid and rifampin.[2]

Bedaquiline is a diarylquinoline that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme necessary for the generation of energy in *Mycobacterium tuberculosis.* This enzyme is essential for the proliferation and survival of the mycobacteria. Bedaquiline comes as 100 mg tablets and must be used only in combination with other anti-mycobacterial medications. It is pregnancy category B based on studies conducted in rats and rabbits; however, due to differences between these animals and humans, the drug should still be used with caution in pregnancy and only when it is really needed. No dose adjustments are needed for mild to moderate hepatic and renal impairments. In cases of severe hepatic and renal impairment, the drug should be used when the benefits outweigh the risks and with caution. The most common adverse drug reactions include nausea, arthralgia, and vomiting.[3]

There are two black box warnings, however, that are associated with bedaquiline which may significantly limit its use. The first is regarding an increased mortality seen in a placebo-controlled trial; 11.4% of patients assigned to be treated with bedaquiline died compared to 2.5% death in the placebo group. Consequently, the drug is only indicated when an effective treatment regimen cannot otherwise be established. Additionally, bedaquiline may cause QTc interval prolongation and as a result, there should be ECG monitoring, caution with other QTc prolonging medications, and the medication should be discontinued if the QT interval reaches greater than 500 milliseconds.[3]

The basis for Bedaquiline's approval was a surrogate marker of sputum conversion time, the time to convert a patient's sputum culture from positive to negative for *Mycobacterium tuberculosis.* In a study of 161 patients, 79% of those on bedaquiline had a negative sputum culture at 24 weeks whereas only 58% of the placebo group had negative cultures. Despite these results, the increase in mortality observed in those who received the drug has raised questions as to the drug's usefulness. Because the drug was approved by the accelerated route based on a surrogate marker, a confirmatory phase III study must be conducted. The FDA has agreed that enrollment may begin in late 2013 or 2014, and the study results are not required until 2022.[4] Janssen Pharmaceuticals expects to begin selling the drug in the second quarter of 2013.[1] Once the drug is on the market and as the phase III study is conducted, the role of bedaquiline in the treatment of multi-drug resistant tuberculosis will become more evident.

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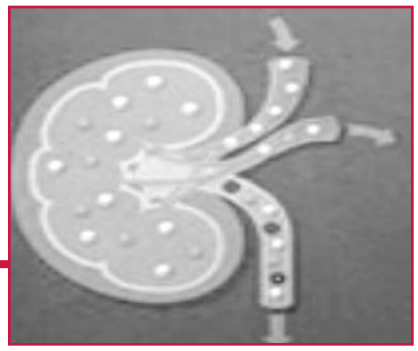
Invokana®: A New First in Class Oral Treatment for Type 2 Diabetes

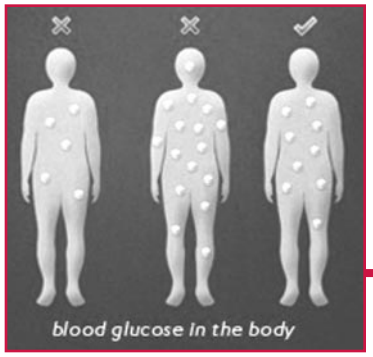
Canagliflozin (Invokana®) is a new first-in-class of oral agents for the treatment of type 2 diabetes approved by the FDA on March 29, 2013. Canagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), which is found in the renal proximal tubules and allows for much of the glucose reabsorption that is filtered through the glomerulus.[1] By inhibiting SGLT2, canagliflozin lowers the renal threshold for glucose, resulting in increased excretion of glucose and better blood glucose control.[1,2] Due to a decrease in plasma glucose concentrations in patients, there could potentially be a decrease in A1C. The SGLT2 protein is also present in the small intestines, which could suggest that canagliflozin may reduce postprandial plasma glucose by inhibiting intestinal absorption of glucose. The increased glucose excretion by the kidneys also results in a loss of calories, which can cause a favorable weight reduction in certain patients.[2,3] Furthermore, the risk for hypoglycemia associated with the drug is particularly low because it is not an insulin secretagogue. There is also an added diuretic effect associated with osmotic diuresis from increased urinary glucose excretion, which can lead to reductions in blood pressure.[3]

Canagliflozin has been studied in combination with other diabetic medications such as metformin, glimepiride, and sitagliptin. When used as monotherapy, canagliflozin 100mg and 300mg reduced A1C by 0.77% and 1.16% respectively.[4] Fasting glucose was also reduced by 37 mg/dL and 44 mg/dL respectively.[2,4] When adding canagliflozin 100 mg once daily to metformin treated type 2 diabetic patients, non-inferiority was shown against glimepiride 6 to 8mg once daily. Also, canagliflozin 300 mg once daily significantly displayed better A1C reductions compared to sitagliptin 100 mg once daily in patients taking a combination of metformin and a sulfonylurea. There are some advantages associated with canagliflozin that may lead to its use amongst diabetic patients.[5]



During clinical trials, patients reduced their systolic blood pressure by 2-8 mmHg and had an average weight loss of about 2-4% of body weight after 6 months of treatment. [2,5]

In addition, there are some disadvantages that are associated with canagliflozin that may limit its use. The FDA had previously raised concerns about the drug's cardiovascular safety and the increased risk of stroke based on the Canagliflozin cardiovascular assessment study (CANVAS)[1,2] There are still ongoing post-marketing studies evaluating malignancies, pancreatitis, bone safety, and pediatric usage. Adverse effects include an increased rate of fungal, genital, and urinary tract infections. It is also contraindicated in patients with a GFR of less than 30 mL/min, end stage renal failure, or on dialysis.[2,4] Dapagliflozin, another SGLT2 inhibitor, was not approved by the FDA in 2012 due to risks of breast and bladder cancers. Other drugs in this class, such as ipragliflozin and empagliflozin, are still in development.[1,3] Therefore, it is evident that canagliflozin may have a place in the pharmacotherapy algorithm for patients suffering from type 2 diabetes when other options have failed.



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Impact of Technology on Healthcare

Technological advancements within the past decade have dynamically revolutionized the way healthcare is being delivered. These advancements involve the manufacturing of drugs and surgical instruments, automated dispensing machinery and Computerized Physician Order Entry (CPOE) / Electronic Health Records (EHR) software used to handle and maintain patients' health records. Furthermore, many healthcare professionals are now able to connect with each other using a simple smartphone application. Some of the benefits seen from these advancements include improvement of patient outcome and quality of life, cutting healthcare costs by decreasing hospital stays and reducing discharge times, reducing medication errors, improving patient adherence and discovering new treatments. In this article, we will focus on the technology involved in hospitals.

Handwritten orders used to be the traditional method to order medications which were faxed/scanned down to the pharmacy for the pharmacist to verify and enter the order to be dispensed. This method has proved to be very inefficient for a number of reasons, most notably medication errors. Poor handwriting resulted in lost time trying to verify the drug name, dose and/or directions. It also played a major role in medication errors because it has been shown that the majority of medication errors occur in the ordering part and one-third occur during the administration process[1]. According to a report on medical errors by the Institute of Medicine, hospital medication errors can cause up to 98,000 deaths annually and cost approximately $38 billion per year.[2] To overcome this major issue, CPOE was introduced. The advent of CPOE made it possible to "generate clear, readable and unambiguous medication orders and has the potential to reduce prescription and transcription errors." It also made it easier to improve order-specific communications and follow-ups as well as track the progress of orders. CPOE also alerts the ordering provider of any potential drug interactions, duplicate medication, an overdose or an allergy[1].

According to USA Today, a survey conducted by a technology security firm found that U.S. hospitals are losing about $8.3 billion annually due to lost productivity and increased patient discharge times[3]. As a result of their proven efficiency and enhanced patient health information security, more hospitals continue to upgrade their EHR systems to keep up with the much-needed technology. Moreover, some hospitals today allow physicians to communicate with nurses via a secured text messaging app using their iPhones instead of using pagers which makes it much more quicker to reach out to physicians. Another survey showed that the U.S. hospital industry loses about $3.2 billion annually in lost discharge time. An average of 37 minutes of discharge time are wasted due to waiting for hospital staff to enter necessary patient information required to release the patient[3].

In conclusion, technology has a significant impact on healthcare and it is our role as healthcare professionals to utilize it to deliver the best healthcare possible to our patients.

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Contributed by:
Mina Malaak, Pharm. D.

Welcome New Pharmacist

Christopher Wheaton, Pharm.D., is a Rutgers Ernest Mario School of Pharmacy 2012 graduate. He is happy to be working as a Staff Pharmacist in the new UH pharmacy department. Outside of work, he enjoys doing outdoor activities.

Lack of SSRI Effectiveness Due to Genetic Variations: Research is Needed

Major Depressive Disorder (MDD) is a mental disorder that is characterized by "sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feeling of tiredness, and poor concentration."[1] MDD in adults in the United States has a lifetime prevalence of 16.5% and a 12-month prevalence of 6.7%.[2] Depression affects 350 million people worldwide and it can lead to suicide which is associated with the loss of about 1 million lives every year. Therefore, depressive disorders are estimated to be the major cause of disability worldwide.[1] MDD can occur as single or multiple episodes. Although common, it is a disabling and serious illness. However, it is treatable by psychotherapy and pharmacotherapy.[3]

About one-third of patients with severe depressive symptoms take antidepressants (ADs).[4] However, with the current ADs available, less than 50% of patients show full remission and only two-thirds show remission after four treatment trials.[5] The lack of full remission or the persistence of residual symptoms predicts a poorer long-term outcome. A study investigating the impact of residual symptoms on treatment-resistant depression, showed the "proportion in remission at the time of follow-up was about 70%, 50%, and 30% of patients discharged in remission, partial remission, and episode, respectively."[6] Therefore, it is important for patients with MDD to receive the correct treatment and achieve full remission during their first treatment in order to improve their long-term probability of remission. This may be done by understanding genetic interactions and thereby improving targeted pharmacotherapy.

Currently, selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for patients with MDD due to their safety in overdose and improved tolerability.[7] SSRIs function by initially blocking the serotonin transporter (SERT). SERT mediates the reuptake of serotonin (5-HT) into the presynaptic terminal, which terminates serotonin neurotransmission. Blocking SERT increases synaptic availability of serotonin. This increased availability stimulates postsynaptic 5-HT receptors and neurotransmission is up-regulated.[8] SERT protein is encoded by a single gene, SLC6A4. The transcriptional activity of SLC6A4 depends on several variations. One of these variations is a repetitive sequence, the SLC6A4-linked polymorphic region (5-HTTLPR). 5-HTTLPR is composed of a short and long version, the short version having lower transcriptional activity.[9] Allelic variation and the differences in transcriptional activity indicate the time it takes to reuptake serotonin from the synaptic cleft and end its neurotransmission. The longer variant leads to faster activity.[10] Many studies show a significant correlation between the presence of the low-expressing 5-HTTLPR short variant and the personality trait, neuroticism. Neuroticism is a trait linked to increased anxiety, stress reactivity, and the probability of developing depression.[9]

Another genetic variation that is also low expressing is the presence of a single nucleotide polymorphism (SNP) located in the long variant of 5-HTTLPR. The low transcriptional activity caused by the SNP of the long variant leads to the long form of 5-HTTLPR functioning as the short form. This results in a slower reuptake of serotonin as is the case in the short allelic form, making the 5-HTTLPR gene triallelic.[10]

The lower expressing allelic forms produce significantly less SERT mRNA and proteins, leading to decreased availability of SERT.[9] Decreased availability of SERT means a decreased number of targets for SSRIs. Hypothetically, less targets for SSRIs makes SSRIs less effective for individuals with the presence of a low expressing genetic variation and also with the higher probability of developing depression.

Verification of the association between genetic variability and decreased effectiveness of SSRIs leads to a more individualized pharmacotherapy approach. Individuals with MDD and the long variant of 5-HTTLPR (not including the SNP) may be ideal for SSRI therapy and are possible faster responders with a higher probability of remission. While those with the low expressing genetic variability (including the short variant and the presence of the SNP on the long variant) are not optimal candidates for SSRIs and less likely to experience a response or remission, these subjects have a decreased rate of serotonin reuptake and neurotransmission termination. Therefore, increased serotonin reuptake is not the problem in patients with low-expressing variants. Other possible problems include low serotonin production and the imbalance

(Continued on page 6)

Lack of SSRI Effectiveness

(Continued from page 5)

between norepinephrine and serotonin transporters. Further studies are needed to identify possible combinations of genetic variants responsible for the effectiveness or lack of effectiveness of SSRIs as well as to identify other possible pharmacotherapy targets in order to improve treatment efforts in the population affected by MDD.

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Bone abnormalities in neonates during prolonged magnesium sulfate use

In the past, magnesium sulfate has been proven to prevent seizures in preeclampsia. However, this past May, the FDA advised health care professionals against using magnesium sulfate injection for more than five to seven days. Continuous administration of magnesium sulfate for preterm labor is no longer FDA approved and no safety and efficacy guidelines are available. Prolonged use has been found to cause low calcium levels and bone problems in the developing baby. Unfortunately, the shortest duration of treatment that can cause these abnormalities is not known. There have been 18 cases of these abnormalities that have been reported to the FDA's adverse event reporting system, in which the average length of exposure was 10 weeks and an estimate of 3,700 grams. Most of these neonates developed osteopenia and fractured bones.

Many of the case reports describing skeletal abnormalities have been previously described in medical literature. Based upon literature, osteopenia and fractures may result from hypermagnesemia which in turn leads to hypocalcemia. One published study showed a statistically significant increase in bone abnormalities in neonate with seven days of exposure compared to three days of exposure. Reports show that lab values resolve within days of birth but the long-term bone effects are unknown because they have not been studied. High blood pressure and high levels of protein in the urine are symptoms of this condition. Alternatives to the magnesium sulfate can include hydralazine to help lower the blood pressure. Some supplements such as calcium, vitamin D, folic acid, and vitamin C may help prevent preeclampsia but do not help once you have the condition. It is important to monitor and watch for any signs of preeclampsia.

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FDA Approves Tecfidera® for Multiple Sclerosis

Multiple Sclerosis is a debilitating autoimmune disease that causes your body's immune system to attack its own myelin sheath that protects the nerves in the brain and spinal cord, thus leading to irreversible damage. It currently has no treatment, therefore all the drugs on the market are used to treat the disease symptomatically. The symptoms vary with the degree of the disease and the location of the damaged nerves. Symptoms include but are not limited to dizziness, fatigue, doubled vision or blurred vision, partial or complete loss of vision usually limited to one eye and accompanied by optic neuritis (pain during eye movement). As a consequence of the damaged nerves, complications such as epilepsy, paralysis, depression, sexual dysfunction, and mental changes arise.[1]

Dimethyl fumarate (Tecfidera®) is an oral drug approved for use in people with relapsing and remitting forms of multiple sclerosis. Its exact mechanism of action is unknown, however it is thought that dimethyl fumarate and its active metabolite, monomethyl fumarate, activate the nuclear factor 2 (Nrf2) pathway in vivo and in vitro. The Nrf2 pathway is known to be involved in the cellular response pathway to oxidative stress, therefore activating this pathway may slow down the damage to the myelin. Dimethyl fumarate is metabolized by esterases into its active metabolite before it goes into the systemic circulation. The active metabolite is then metabolized by the tricarboxylic acid cycle and does not involve the cytochrome p450 system. The drug is also excreted by exhaling carbon dioxide and therefore does not require renal or hepatic dose adjustment.[2]

Biogen Idec, the company responsible for the discovery of dimethyl fumarate, announced that the drug significantly reduced relapses and damage associated with relapses. The DEFINE trial, a phase 3 double-blind, placebo-controlled, randomized trial, yielded successful results. The study found that dimethyl fumarate decreased the proportion of patients who relapsed by 49 to 50% over two years and it also decreased the annual relapse rate and the risk of disability progression. In addition to activating the Nrf2 pathway, research has also shown that Tecfidera may acitvate cytoprotective effects in the cell.[3] The second randomized, double-blind, placebo-controlled phase 3 trial, CONFIRM, also showed positive results. The CONFIRM trial used glatiramer acetate (Copaxone®), a 20 mg subcutaneous injection, as a comparison drug. The study showed that dimethyl fumarate was more effective at reducing the annual relapse rate (ARR), with dimethyl fumarate reducing the ARR by 44% with twice-a-day dosing and by 51% with three times-a-day dosing. Glatiramer only reduced the ARR by 29% compared to placebo during the two year trial.[4]

Although Tefidera shows considerable promise, the drug has its disadvantages. Flushing was reported in 35% of people in the active drug group verses only 5% of placebo group. Although adverse effects such as diarrhea, nausea, and upper abdominal pain were reported more frequently in the dimethyl fumarate study group, the overall incidence of these effects was not drastically increased in these groups versus the placebo study group. The highest incidence of adverse events were also reported within the first month of treatment and gradually decreased after that.[3] It was also discovered that dimethyl fumarate may decrease lymphocyte count up to 30% in the first year of treatment. Despite this effect, the dimethyl fumarate study groups in the clinical trials did not show an increased risk of infections compared to placebo.[2] Though the safety of the drug will be more thoroughly evaluated in post market studies, dimethyl fumarate (Tecfidera®) shows great promise in improving the overall quality of life of Multiple Sclerosis patients despite the continued absence of a cure for this disease.

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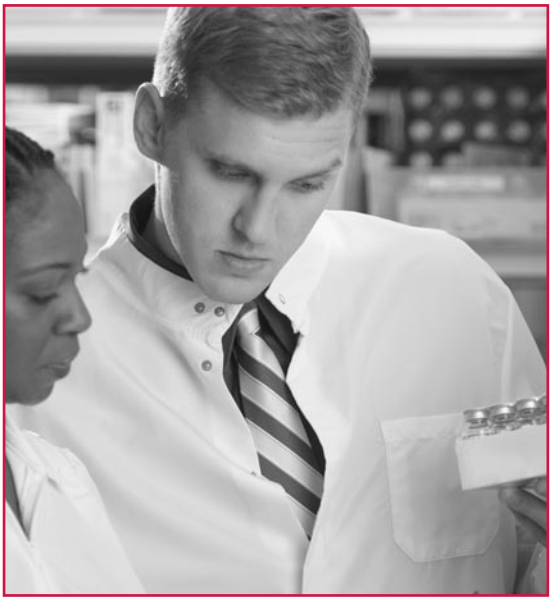
Pharmacists and Nurses role in minimizing PCA adverse events

A patient underwent surgical repair of a heel injury. Within 15 minutes of his arrival, he received IV doses of meperidine, morphine, and fentanyl for pain. The patient's surgeon then ordered PCA (Patient Controlled Analgesia) of morphine 1mg/mL, 3 mg per demand dose, a lockout of 10 minutes and a basal rate of 1mg/hour. The patient's weight was not taken into consideration when calculating the PCA morphine dose nor for the other two medications. The nurses did not follow the correct protocol in terms of taking proper care of the patient, measuring his pain scale and oxygen saturation levels and educating the patient on how to use the PCA device appropriately. Six hours later, the patient went into respiratory distress.



PCA is a user-controlled method of pain management which utilizes a device that can be programmed to deliver a set dose of medication upon patient demand using a hand-held control mechanism. PCAs have been shown to improve pain management, however if protocol is not followed, they could be fatal. According to a U.S. Pharmacopeia examination done in 2003, an improper dose/quantity of PCA had the highest percentage error of 38.9%. Other errors included wrong drug preparation, wrong dosage form or route, and expired products. The role of pharmacists and nurses in PCA management is a very important aspect in the administration and proper pain management of a patient.

A policy/procedure for PCA has been implemented at University Hospital to help ensure its proper handling and administration. Step two of the policy states that a pharmacist must "verify [the] physician order for drug, concentration, bolus, mode, four-hour dose limit, and lockout interval. A Pharmacist also must ensure that all other PRN and continuous infusions of opioid analgesics and sedatives have been discontinued." Following this step would minimize the amount of drug dosage errors that would occur. After proper verification, nurses should double-check that the medication is correct and is being administered to the correct patient.

In the case above, the nurses did not properly educate the patient on how to use the device. University Hospital policy states that the nurse must "explain the purpose of PCA and PCA pump operation in age and developmentally appropriate terminology. "For example, only the patient is allowed to press the PCA button. Family members or anyone else in the room are not allowed to press the button for the patient". Providing patient education allows them to fully understand how much medication they can self-administer and how to do it properly to avoid an overdose or malfunction of the machine.

As far as monitoring, there are several necessary steps that have to be considered during the time the PCA is administered. Nurses must monitor vital signs every hour for the first four hours, followed by every two hours for the next four hours and then every four hours after until the PCA is discontinued. This is to ensure that patient is tolerating the opioid being administered. All steps taken in monitoring a patient whether it be checking vital signs, RASS (Richmond Agitation Sedation Scale), or pain scale must be recorded in a PCA/PCEA Flow sheet. This prevents duplicate dosing, overdosing or under-monitoring.

Computerized Prescribers Order Management (CPOM) has helped reduce the amount of errors as well. It has given pharmacists and nurses choices and options to choose from rather than written out the full order by hand which leaves room for transcription errors. If the nurses and pharmacists are properly educated on these procedures, errors and deaths can be significantly decreased. Hopefully, PCA devices will provide more of a therapeutic benefit for the patient than adverse events in future cases.

References:

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