



Shaukat Khanum Memorial Cancer Hospital and Research Center

Pharmacy Newsletter

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The Team

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P&TC UPDATES:

Following drugs have been approved by P&TC:

1. **Rivaroxaban Tab 10mg.** Approved as regular formulary item
2. **Duloxetine Cap 30 mg.** Approved as regular formulary item
3. **Paroxetine Tab 12.5 mg.** Restricted by service (Psychiatrist only)
4. **Paliperidone Tab 1.5 mg XR.** Restricted by service (Psychiatrist only)
5. **Milrinone Inj 10mg.** Approved as regular formulary item

CANAGLIFLOZIN: Not Good For Limbs

Based on new data from two large clinical trials, the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo. *The CANVAS trial showed that over a year's time, the risk of amputation for patients in the trial were equivalent to 5.9 out of every 1,000 patients treated with canagliflozin and 2.8 out of every 1,000 patients treated with placebo. The CANVAS-R trial showed that over a year's time, the risk of amputation for patients in the trial were 7.5 out of every 1,000 patients treated with canagliflozin 4.2 out of every 1,000 patients treated with placebo.* Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs. Before starting canagliflozin, health care professionals should consider factors that may predispose patients to the need for amputations. These factors include a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.

Neal, Bruce, et al. "Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)—a randomized placebo-controlled trial." *American heart journal* 166.2 (2013): 217-223.

ISCHEMIC EVENTS WITH CISPLATIN – A REVIEW OF SKMCH PATIENTS

Cisplatin based regimens are associated with major adverse effects of nephrotoxicity and myelotoxicity; however, significant reports of adverse cardiac events have been observed as well. Increased apoptosis and oxidative stress are considered as major causative mechanisms with some hypothesis stating hypomagnesemia and levels of von Willebrand factor as the cause.¹ A retrospective chart review of 271 patients at Princess Margaret Hospital between 1986 and 1996 reported vascular events in 35 patients (12.9%) receiving chemotherapy; 77% of these adverse events occurred during the first 2 cycles of chemotherapy and 3 events led to death.² Another study evaluated the long-term risk of cardiovascular disease in survivors of testicular cancer. BEP (bleomycin, etoposide, cisplatin) chemotherapy regimen had a 5.7 fold higher risk (95% CI: 1.9–17.1) of coronary artery disease compared with surgery alone and a 3.1-fold higher risk (95% CI: 1.2 –7.7) of myocardial infarction (MI).³

SKMCH&RC report presents 4 out of 2233 patients identified through a retrospective chart review of patients who received cisplatin-based combination chemotherapy from January 2017 through May 2017. 3 (75%) of these patients had cardiac risk factors. 2 (50%) patients were with normal magnesium levels while magnesium levels were not available for 2 (50%) patients.

Incidence of MI with cisplatin in SKMCH patients is very low (0.001%); however patients with known coronary risk factors should be evaluated and treated with caution.

MI with Cisplatin chemo regimens – SKMCH Data Review Jan, 2017 – May, 2017

Sr. No.	Tumor type	Age	Treatment	Vascular complications	Risk factors	Interval from last treatment	Serum magnesium
1	Seminoma	39	BEP	Myocardial infarction	Occasional smoker	2 days (2 nd cycle)	2.58
2	MGCT	23	BEP	Myocardial infarction	IHD family history	1 day(3 rd cycle)	2.04
3	Nasopharyngeal carcinoma	65	Cis/Gem	Myocardial infarction	Family history of HTN	1 day(2 nd cycle)	NA
4	Lower alveolus carcinoma	53	Cis/Gem	Myocardial infarction		1 day (1 st cycle)	NA

BEP: Bleomycin, Etoposide, Cisplatin; Cis/Gem: Cisplatin/ Gemcitabine; IHD: Ischemic heart disease; MI: Myocardial infarction, HTN: Hypertension; MGCT: Mixed germ cell tumor; NA: Not available

¹. Schwarzer S, Eber B, Greinix H, et al: Non-Q-wave myocardial infarction associated with bleomycin and etoposide chemotherapy. *European Heart Journal* 1991; 12:748-750.

². Czaykowski PM, Moore MJ, Tannock IF. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. *J Urol* 1998; 160: 2021-2024.

³. Haugnes H, Wethal T, Aass N et al. Cardiovascular Risk Factors and Morbidity in Long-Term survivors of Testicular Cancer: A 20-Year Follow-Up Study. *J Clin Oncol* 2010; 28(30): 4649-4657

Biomarker Based FDA Approval of Anticancer Drug – The First of Its Kind

For the first time in history of cancer treatment, a drug has been FDA-approved based on a tumor’s biomarker (specific genetic marker) without regards to the tumor’s original location, such as with breast cancer. Pembrolizumab (Ketyruda) can now be used for the treatment of patients with un-resectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This use includes patients who have failed therapy with no

alternatives and those with advanced colorectal cancer who failed on certain chemotherapy drugs. Standard 50 mg vial cost \$ 2300. Keytruda is not available in Pakistan.

Released on May 23, 2017, U.S. Food and Drug Administration

PARTIAL OPIOID OF CHOICE – A COMPARISON

	TRAMADOL	PETHIDINE	NALBUPHINE
Potency	10% less than that of morphine	7.5 times less than that of morphine	Equal to morphine
Respiratory depression	+	++	+++
Route of administration	PO/IV/IM/SC	IV/IM	IV/IM/SC
Seizures potential	+++	++	-
Maximum dose/day	400mg (600mg for palliative analgesia)	600mg	160mg
Dosing in pediatrics	1-2mg/kg/dose (not recommended below 17 year of age)	1-1.8mg/kg/dose (max single dose of 100mg)	0.1-0.2mg/kg/dose (max single dose of 20mg)
Renal dose adjustment	CrCl <30ml/min Increase dosing interval to q12h, (max 200mg/day)	CrCl <10 ml/min administer 50% of recommended dose. (max 200mg/day)	CrCl <80ml/min, use with caution
Frequency (duration of analgesia)	Usual q8h, (6-8 hours)	Usual q4h, (2 to 4 hours)	Usual q6h, (3-6 hours)
Cost comparison	\$\$	\$	\$\$\$

The ceiling effect for respiratory depression with nalbuphine provides a unique safety factor among potent analgesics. Nalbuphine causes maximum respiratory depression at dose of 30mg; any dose above 30mg would not add further to the respiratory depression.¹

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking selective serotonin reuptake inhibitors, tricyclic antidepressants, opioids, monoamine oxidase inhibitors and neuroleptics. Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections).

In tramadol overdose, naloxone administration may potentiate the risk of seizures. Nalbuphine produces better pain relief and hemodynamic stability in postoperative period in patients undergoing orthopedic surgeries when compared to tramadol which is associated with more nausea, vomiting and requirement of rescue analgesia. Pethidine has shown superior analgesia as compared to tramadol in post-operative pain; however sedative potential is higher.²

¹Romagnoli, A. and Keats, A. S. (1980), Ceiling effect for respiratory depression by nalbuphine. *Clinical Pharmacology & Therapeutics*, 27: 478–485. doi:10.1038/clpt.1980.67

²R N Solanki et al. "A Comparative Study of Intravenous Nalbuphine HCl and Tramadol HCl for Post Operative Pain Relief Following Orthopaedic Surgeries", *Asian Pac. J. Health Sci.*, 2015; 2(1): 155-160

BIOSIMILARS

Therapeutic equivalent generic drugs are often major cost savers for hospitals and patients as well as profitable for the pharmaceutical industry, which makes one question why we do not have access to generic versions of biologic drugs such as Trastuzumab (Herceptin), Rituximab (Mabthera), and Cetuximab (Erbix) etc. The term “generic” should not be used to describe a similar biologic product. The more appropriate term is “biosimilar”, which describes that the biological product is highly similar to the reference biologic product (RBP) notwithstanding minor differences in clinically inactive components; and there is no clinically meaningful difference between the biological product and RBP in terms of the safety, purity, and potency. Compared to Biosimilars, “generic” products are the exact same as the brand in the dosage, safety, strength, quality, and contains identical amount of the same active ingredient(s) as the brand.

One major challenge in manufacturing of biosimilars is the patented nature of the process for developing and manufacturing the original product. The biologic manufacturing process cannot be exactly duplicated by another manufacturer, thus the active ingredient can only closely resemble the RBP but may not be identical. Although the Biologics Price Competition and Innovation Act of 2010 allows the US FDA to develop pathways to approve biosimilar products, the guidelines are still in development as to exactly how a biosimilar will be assessed and approved. In addition, a unique pathway is needed to appropriately assess biosimilars and to ensure they are highly similar to the RBP. Similarly, few of the newer biosimilars have not been shown to be similar (or have not been duly assessed) in all three fundamental areas (quality, efficacy and safety) to a licensed RBP as defined by WHO guidelines called as non-comparable biosimilar. Moreover, increased emphasis on identification and tracking of biosimilars in pharmacovigilance systems has been required by European regulators and it states that “.... *all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with regulation....*”. These factors make the production of biosimilars a challenge for pharmaceutical companies.

The SKMCH P&TC has approved the guidelines that only US FDA and European Medicines Agency (EMA) authority’s list of approved biosimilars will be used in the hospital. Analysis estimates that there are \$60 billion worth of biological products expiring by 2020, with the expectation that this cost saving will be passed down to the patients through biosimilars. It will be interesting to see how the drug regulatory authority of Pakistan including relevant institutions will handle the issue with biosimilar approval and regulate the interchangeability.

Muhammad Tahir Aziz

AMITRIPTYLINE & CNS ACCESS OF DRUGS

New research by NIH, USA found that pairing the antidepressant amitriptyline with drugs designed to treat central nervous system diseases, enhances drug delivery to the brain by inhibiting the blood-brain barrier in rats. According to Ronald Cannon, Ph.D., staff scientist at NIH, the biggest obstacle to efficiently delivering drugs to the brain is a protein pump called P-glycoprotein. Located along the inner lining of brain blood vessels, P-glycoprotein directs toxins and pharmaceuticals back into the body's circulation before they pass into the brain. Cannon and his colleagues found that amitriptyline significantly reduced P-glycoprotein's pump activity in brain capillaries within 10-15 minutes. When amitriptyline was removed, P-glycoprotein pump activity returned to full-strength. *Though the observations are based on animal studies, researchers strongly anticipate that administering amitriptyline along with a lower dose of an opioid could relieve pain and reduce the negative side effects, such as constipation and addiction, usually seen with higher doses of prescribed opioids.*

News release Thursday, April 27, 2017 National Institute of Health, USA