Shaukat Khanum Memorial Cancer Hospital and Research Center

Pharmacy Newsletter

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A Word about Buprenorphine

Provided the current shortage of oral morphine, buprenorphine is an excellent alternative opioid analgesic to use in our patients. With high affinity at the μ-, κ- and δ- opioid receptors, subjective and physiological effects are generally similar to morphine. Antagonist effects at the κ-opioid receptor may limit spinal analgesia, sedation and psychotomimetic effects. The ceiling dose for analgesia in humans is much higher than the maximum recommended dose of 3.36mg/day. Sublingual (SL) buprenorphine is rapidly absorbed into the oral mucosa (2–3min), followed by a slower absorption into the systemic circulation. With typical clinical doses, it is possible to use morphine (or other μ-opioid receptor agonist) for breakthrough pain and to switch either way between buprenorphine and morphine (or other μ-opioid receptor agonist) without loss of analgesia. SL buprenorphine is about 80 times more potent than oral morphine; in round figures 0.4mg SL buprenorphine is equivalent to 30mg PO morphine. Usual recommended dose is 0.2 – 0.4mg SL q6-q8hrs. It is a substrate of CYP3A4 and concomitant use of drugs like fluoxetine, clarithromycin, ketoconazole and carbamazepine needs to be watched out for. Due to high receptor affinity and relative potency, naloxone in standard doses does not reverse buprenorphine induced respiratory depression. In case of toxicity, it is recommended to give 2mg naloxone stat IV over 90 seconds, followed by continuous IV infusion of 4mg per hour till the condition is satisfactory (usually less than 90 minutes). Buprenorphine is available as 0.2mg sublingual tablets in our hospital pharmacy.

Ref: Draft v 1.0. Palliative drugs.com. Newsletter Nov/Dec 2006. BNF 4.7.2

Dacarbazine ADRs at SKMCH&RC

Dacarbazine is an anti-cancer with very high consumption at SKMCH&RC provided its documented benefit in hodgkin's lymphoma. We had increased incidence of allergic skin reactions with dacarbazine infusion in pediatric cancer patients in August and September this year (total of 5 cases were reported). Data is presented as follows:

Patient	1	2	3	4	5
Diagnosis	Hodgkin lymphoma stage IIIAS	Hodgkin lymphoma stage IIIB	Hodgkin lymphoma stage IIIAS	Hodgkin lymphoma stage IIA	Hodgkin lymphoma stage IIA
Chemotherapy Regimen	COPDAC	ABVD	COPDAC	ABVD	ABVD
Dose (mg/m²)	250 mg/m²	375 mg/m²	250 mg/m²	375 mg/m²	375 mg/m²
Date	18-08-2017	18-08-2017	18-08-2017	18-08-2017	05-09-2017
Time	19:00	16:00	20:00	21:00	20:00
Type of allergic reaction	Shivering	Fever, shivering, tachycardia & hypertension	Shivering	Shivering	Fever with shivering

COPDAC: Cyclophosphamide, vincrisitine, prednisolone, dacarbazine. ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine

A thorough review of dacarbazine use and response was carried out. A total of 418 injections have been used during the report period. There have been no reports of allergic reactions in adult patients, while the overall incidence of dacarbazine allergic reactions is 0.009%. Official literature mentions a <1% incidence of allergic reactions with infusion. As a precautionary measure, it is suggested to avoid rapid infusion of the drug. Dacarbazine should be infused ideally over 1-2hrours with infusion bag not varying much from body temperature. Pheniramine & hydrocortisone should be used as secondary prophylaxis for subsequent dosing in patients suffering allergic reaction with initial dose.

Ref: www.cancercareontario.ca/drugformulary/drugs/monograph/28656

Paralytic of choice – a comparison

	PANCURONIUM	VECURONIUM	ROCURONIUM	*ATRACURIUM	CISATRACURIUM
Onset(min)	3-5	3-5	1-2	3-5	3-5
Duration(min)	60-90	20-35	20-35	20-35	25-30
Recovery index (min)	30-40	10-15	8-12	10-15	12-15
Elimination route	Renal	Hepatic	Hepatic	Hepatic	Hepatic
Histamine release	No	No	No	Yes	Much less likely than atracurium
Vagolytic activity	Yes	Yes at higher doses	Yes at higher doses	No	No
Prolonged weakness	No	Yes	No	No	Yes
Seizure activity	No	No	No	Yes	No
Anaphylaxis	No	No	No	Yes	No
Relative cost	$	$	$	$$$	$$

**Hospital formulary drug.*

Ref:Online.lexi.com
Greenberg, Steven B., and Jeffery Vender. "The use of neuromuscular blocking agents in the ICU: where are we now?." Critical care medicine 41.5 (2013): 1332-1344.Papazian, Laurent, et al. "Neuromuscular blockers in early acute respiratory distress syndrome." N Engl J Med 363.12 (2010): 1107-1116.

Perioperative Antibiotic Use at SKMCH&RC

Peri-operative antibiotic use has been minimized internationally to avoid unnecessary antibiotic use. We conducted a prospective review of antibiotic use in surgery patients at SKMCH for the month of July to August, 2017. In a total of 64 patients, average duration of antibiotic use was 3.5 days (Fig: 1). Total number of clean surgical procedures was 54, with 3.4 average number of post-surgery antibiotic use days (Fig: 1). Duration ranged from 0 to a maximum of 15 days in total. In a total of 10 dirty surgical procedures, average antibiotic use duration was 3.6 days with the range of 0 to 10 days maximum. 29 cases (45.3%) had antibiotic use in accordance with the guidelines, while 35 cases (54.7%) had antibiotic use duration against the guidelines (Fig: 2). Of the total studied cases, 2 cases presented with documented bacterial infection post-surgery (1 case of total knee replacement and 1 case of gastrectomy respectively). We had 26 cases of mastectomy all with normal post-operative hemodynamic parameters. Average duration of antibiotic use in mastectomy was 3.07 days with co-amoxiclave as the antibiotic used in all cases. Piperacillin-Tazobactam was chosen as prophylactic antibiotic in a total of 6 cases (2 whipples, 1 pulmonary decortication, 2 esophagectomy, one hepatic partitioning procedure respectively).

In view of the standard recommendations, antibiotic use can be cut down on surgery patients as a cost effective option. It is recommended to avoid successive antibiotic dosing especially in clean surgery cases to avoid unnecessary antibiotic use, risk of resistance and associated adverse effects.

Figure: 1

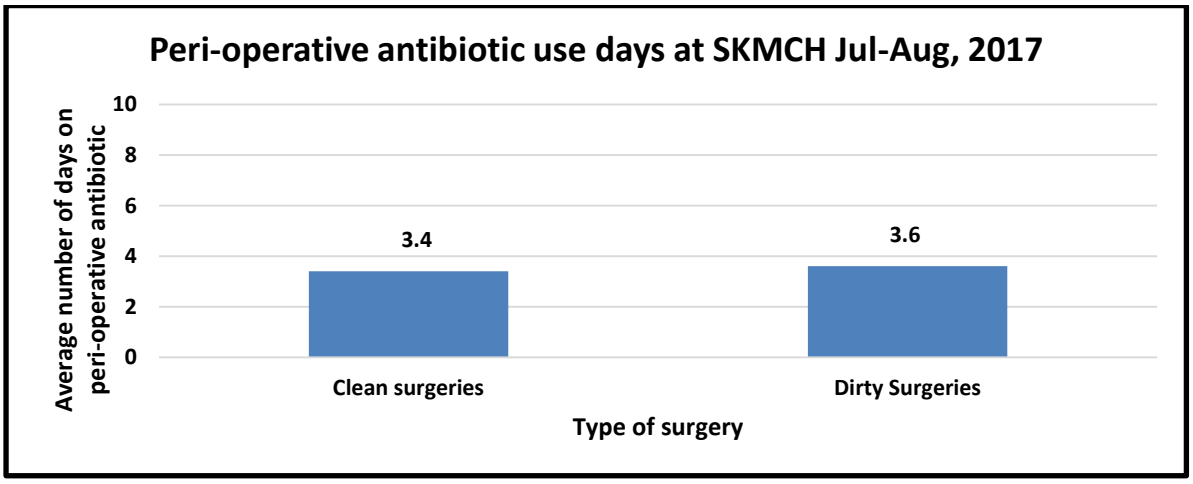
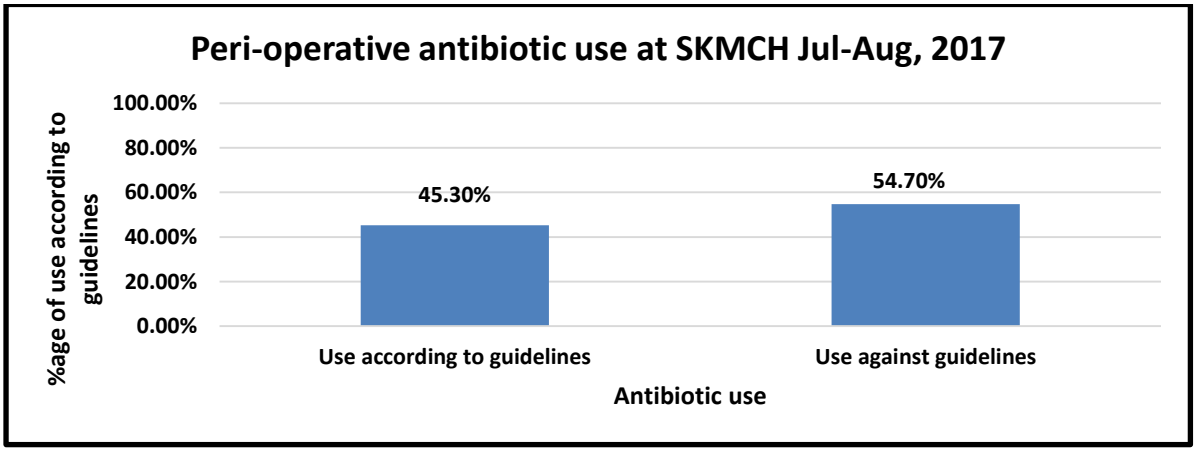


Figure: 2



Ref: "Clinical practice guidelines for antimicrobial prophylaxis in surgery". ASHP therapeutic guidelines Pg 624-675

NEWS & UPDATES

Neratinib as extended adjuvant treatment for early stage HER-2 positive breast cancer

FDA has recently approved neratinib to be used in patients with early stage HER-2 amplified breast cancer for extended adjuvant treatment to follow adjuvant trastuzumab-based therapy. Women with early-stage HER-2 positive breast cancer and within two years of completing adjuvant trastuzumab, were randomized to receive either neratinib or placebo for one year. Invasive disease free survival (iDFS) was 94.2% in patients treated with neratinib compared with 91.9% in those receiving placebo after two years. Recommended dose is 240mg given orally once daily with food, continuously for one year along with an antidiarrheal prophylaxis to be considered with first dose and continued during the first two cycles of treatment and as needed thereafter. Common adverse effects leading to discontinuation were diarrhea and hepatotoxicity, which were found to be 16.8% and 1.7% of cases respectively. Drug is not registered in Pakistan as yet.

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

Delafloxacin: New antibiotic for bad bugs

Delafloxacin is a new generation fluoroquinolone approved by FDA in 2017. It is specifically indicated in adults with acute bacterial skin and skin structure infections (ABSSSIs) caused by certain gram-positive and gram-negative pathogens, including methicillin-resistant ***Staphylococcus aureus*.** In a double-blind, Phase 2 trial, 256 patients were randomized (1:1:1) to 300 mg of delafloxacin, 600 mg of linezolid or 15 mg/kg vancomycin (actual body weight), each administered intravenously twice daily for 5–14 days. Cure rates were significantly greater with delafloxacin versus vancomycin (mean difference: −16.3%; 95% CI, −30.3% to −2.3%; P=0.031); differences were significant for obese patients (BMI ≥30 kg/m^2; mean difference: −30.0%; 95% CI, −50.7% to −9.3%; P=0.009), but not for non-obese patients. Cure rates with delafloxacin and linezolid were similar. Percentage decrease in total erythema area was significantly greater with delafloxacin versus vancomycin at follow-up (−96.4% versus −84.5%; P=0.028). There was no difference in bacterial eradication among the treatment groups. Dose adjustments are required in case of renal and hepatic failure. Delafloxacin is associated with neuropathy, tendon rapture and impaired cartilage growth. Most common side effects are GI disturbance and elevation in liver enzymes. Anticipated availability is currently undetermined.

Ref: Kingsley, Jeff, et al. "A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin." Journal of Antimicrobial Chemotherapy 71.3 (2015): 821-829.

Dealing with complicated UTI: What's new on FDA list?

The FDA has approved intravenous Vabomere (meropenem and vaborbactam) for adults with complicated urinary tract infections (cUTI), including pyelonephritis caused by specific bacteria. In a study with 545 adults with cUTI, including those with pyelonephritis caused by susceptible microorganisms: Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae species complex in adults, 98% of patients had a cure or improvement in symptoms and a negative urine culture test approximately 7 days after completing treatment. 77% of patients treated with Vabomere compared with 73% of patients treated with piperacillin/tazobactam had resolved symptoms and a negative urine culture. The most common adverse reactions in patients taking the antibiotic were headache, infusion site reactions and diarrhea while the drug also carries risk of seizures. Anticipated availability in US is fourth quarter of 2017.

*Ref: Released on August 29, 2017 **U.S. Food and Drug Administration***