



Shaukat Khanum Memorial Cancer Hospital and Research Center

# Pharmacy Newsletter

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## **Calcium (Ca) and Phosphorus (PO<sub>4</sub>) prescribing in TPN**

Ca and PO<sub>4</sub> dosing needs consideration for incompatibility in TPN solution. If mixed in too high a concentration, Ca and PO<sub>4</sub> may form insoluble calcium phosphate precipitates. Keeping the Ca: PO<sub>4</sub> ratio greater than 1:2 (mg: mg) is recommended, while few sources suggest a Ca: PO<sub>4</sub> ratio of 1.7:1 (mg:mg) in TPN, keeping total amount of Ca and PO<sub>4</sub> ≤ 45meq/L. For instance, 15 mEq of Ca ion and 30 mEq of PO<sub>4</sub> ion per liter is a generally accepted dose. Amino acids form soluble complexes with Ca and PO<sub>4</sub> and provide a buffer to maintain a lower pH to prevent Ca and PO<sub>4</sub> precipitation. So a protein free TPN may not be a good medium for addition of Ca & PO<sub>4</sub>; Separate replacement of PO<sub>4</sub> may be a better option in this case. Recommended concentration of amino acids in TPN is 2.5% or more to avoid Ca/PO<sub>4</sub> incompatibility.

*Ref: Am J Health-Syst Pharm. 2008; 65:73-8*

## Therapeutic Drug Monitoring Recommendations for Warfarin

### Initiating Warfarin Therapy

- Initiate therapy with the estimated daily maintenance dose (2-5 mg.).
- Elderly or debilitated patients often require lower daily doses of warfarin (2-4 mg.).
- Patients may be confused by alternating daily doses (e.g. 7.5 and 5.0 mg).
- Significant changes in INR can usually be achieved by small changes in dose (15% or less).
- 4-5 days are required after any dose change, any new diet or drug interaction to reach the new antithrombotic steady state.

INR TARGETS	
<b>Disease</b>	INR range
<b>DVT/PE</b>	2.0-3.0
<b>Atrial Fibrillation</b>	2.0-3.0
<b>Myocardial Infarction</b>	2.0-3.0
<b>Mechanical Heart Valve</b>	2.5-3.5

		Day 1	Day 2	Day 3		Day 4 & after	
<b>In-patient Anticoagulation</b>	Warfarin Dose	5 mg	5 mg	2-5 mg	INR **	2-5 mg	INR*
<b>Out-patient Anticoagulation</b>	Warfarin Dose	2-5 mg	2-5 mg	2-5 mg		2-5 mg	

\* Should be overlapped for 3-5 days with heparin in cases with active thrombosis

\*\* Starting on day 3, adjust subsequent doses as outlined below based on INR. Obtain INR 3-4 times in week 1; twice in 2nd week; then weekly until stable; then monthly. Elderly or debilitated patients often require lower daily doses of warfarin (2-3 mg).

INR	Days			
	3	4	5	6
	Dosage			
<1.5	5.0 - 10.0 mg	10.0 mg	10.0 mg	7.5 - 12.5 mg
1.5-1.9	2.5 - 5.0mg	5.0 - 7.5 mg	7.5 - 10.0 mg	5.0 - 10.0 mg
2.0-3.0	0.0 - 5.0 mg	0.0 - 5.0 mg	0.0 - 5.0mg	0.0 - 7.5 mg
>3.0	0.0	0.0	0.0	0.0

### Stable Patients: Dosing algorithm to achieve INR of 2.0 - 3.0

Warfarin Sodium: Monitoring and dose adjustment in stable anti-coagulated patients  
(Based on a starting dose of 4 mg/d)

INR	Action
>10.0	Stop warfarin. Contact patient for examination.
7.0-10.0	Stop warfarin for 2 days; decrease weekly dosage by 25% or by 1 mg/d for next week (7 mg total); repeat PT in 1 week.
4.5-7.0	Decrease weekly dosage by 15% or by 1 mg/d for 5 days of next week (5 mg total); repeat PT in 1 week.
3.0-4.5	Decrease weekly dosage by 10% or by 1 mg/d for 3 days of next week (3 mg total); repeat PT in 1 week.
2.0-3.0	No change.
1.5-2.0	Increase weekly dosage by 10% or by 1 mg/d for 3 days of next week (3 mg total); repeat PT in 1 week.
<1.50	Increase weekly dose by 15% or by 1 mg/d for 5 days of next week (5 mg total); repeat PT in 1 week.

INR: International normalization ratio, PT: Prothrombin time

Contra-indications: Pregnancy, history of warfarin-induced purpura, active bleeding

Ref: <https://www.careinternet.net/caregiver/warfarin.php>

## COPADM in UKCCSG NHL Group

Chemotherapy dosing and schedule vary in multiple COPADM protocols. Summary is provided for clarification.

- **Induction phase** has COPADM1 & COPADM 2.
- Cyclophosphamide 250mg/m<sup>2</sup> BID (500mg/m<sup>2</sup>/day) D2-D4 in COPADM 1 of induction phase.
- Cyclophosphamide 500mg/m<sup>2</sup> BID (1000mg/m<sup>2</sup>/day) D2-D4 in COPADM 2 of induction phase.
- Triple intrathecal chemo drugs (MTX, Cytarabine & Hydrocortisone) are scheduled on D2, D4 & D6.
  
- **Maintenance phase** has 4 cycles in total. COPADM is cycle 1 of maintenance phase
- Cyclophosphamide is 500mg/m<sup>2</sup> OD (500mg/m<sup>2</sup>/day) D2-D3
- Triple Intrathecal drugs are scheduled on D2 & D3

Ref: UKCCSG NHL Group Guidelines for the Management of Burkitt/Burkitt like and B large cell Non-Hodgkin Lymphoma 2003

## Immunoglobulin G Infusion Guidelines

Immunoglobulin G (IgG) has labeled indications for primary immunodeficiency (400mg/kg first dose with maintenance dose of 200-400mg/kg once a month), idiopathic thrombocytopenic purpura (400mg/kg for 5 days followed by a maintenance dose of 400mg/kg once a week), severe infections (200-400mg/kg/day for 2-3 days) and Kawasaki syndrome (2g/kg as single dose). Infusion reactions have been reported with faster rates. While initiating, the infusion rate should be 1 ml/min (about 20 drops/min); if there is no adverse reaction for the first 15 minutes, the infusion rate can be increased. However, the rate should not exceed 3 ml/min (about 60 drops/min). IgG is available as a 2.5g injectable vial with an approximate cost of PKR 20,000 per vial.

Ref: Product literature

## Different but not better! Comparative effectiveness of Haloperidol and Quetiapine in treatment of delirium

A single blind, randomized controlled study of adult ICU patients (n=70 with 32 patients in haloperidol group and 31 patients in quetiapine group) revealed that quetiapine is as effective as haloperidol in treating delirium. With flexible dosing regimen being tested (haloperidol: 0.25-1.25 mg; quetiapine 12.5-75 mg/d), Delirium Rating Scale-Revised-98 (DRS-R-98) and Mini Mental Status Examination (MMSE) were the primary and secondary efficacy measures respectively. At the end of the trial, 68.75% and 67.74% of subjects had mean DRS-R-98 scores below 10 in the haloperidol and quetiapine group respectively. By 6<sup>th</sup> day, 12 (37.5%) patients in haloperidol group and 9 (29.03%) patients in the quetiapine group had DRS-R98 score of "0" with no significant difference between the two groups ( $P = 0.47$ )

Ref: Grover, S., Mahajan, S., Chakrabarti, S., & Avasthi, A. (2016). Comparative effectiveness of quetiapine and haloperidol in delirium: A single blind randomized controlled study. *World Journal of Psychiatry*, 6(3), 36g

## Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Diabetes confers an increased risk of adverse cardiovascular and renal events. In EMPA-REG OUTCOME trial, patients with type-2 diabetes mellitus, with baseline GFR of 30 ml per minute per 1.73 m<sup>2</sup> of body-surface area were randomized to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily.

**Incident or worsening nephropathy** occurred in 12.7% of empagliflozin group and in 18.8% of placebo group (hazard ratio in the empagliflozin group, 0.61; 95% confidence interval, 0.53 to 0.70;  $P < 0.001$ ). **Doubling of the serum creatinine level** occurred in 1.5% of empagliflozin group and in 2.6% of placebo group, a significant relative risk reduction of 44%. **Renal-replacement therapy** was initiated in 0.3% of empagliflozin group and 0.6% of placebo group, representing a 55% lower relative risk in the empagliflozin group. In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care.

Ref(EMPA-REG OUTCOME Clinical Trials July 28, 2016)

## News & Update

**Bezlotoxumab** (*Toxin B neutralizing antibody*): Approved by FDA in Oct, 2016. Bezlotoxumab is indicated to reduce recurrence of *Clostridium difficile* infection (CDI) in adult patients receiving anti-bacterial drug treatment for CDI who are at high risk of recurrence. It is not an anti-bacterial drug and should only be used in conjunction with anti-bacterial treatment of CDI. Bezlotoxumab will be marketed internationally by brand ZINPLAVA (25mg/ml) under MERCK in first quarter of 2017.

**Olaratumab** (*PDGFR –Alfa blocker*): Approved for the treatment of soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate. Not registered in Pakistan.

**Atezolizumab** (*PD-L1 blocker*): Approved for patients with urothelial carcinoma and metastatic non-small cell lung cancer whose disease progressed during or following platinum-containing chemotherapy. Standard dosing is 1200mg IV every 3 weeks, continued until disease progression or unacceptable toxicity. International price of one 1200mg vial is \$10,500 approximately.\* Not registered in Pakistan.

**Venetoclax** (*Bcl2 inhibitor*): Approved for the treatment of chronic lymphocytic leukemia with 17p deletion. Started at low dose of 50mg per week, Venetoclax dose is escalated by 50mg weekly to maintenance dose of 400mg and continued until disease progression or unacceptable toxicity. Not registered in Pakistan; International price of one 50mg tablet is \$50 approximately. Standard maintenance dose of 400mg will cost \$200 approximately.\*

**Eribulin** (*Microtubule targeting agent*): Approved for the treatment of patients with un-resectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. It is dosed as 1.4mg/m<sup>2</sup> at D1 & D8 of a 21 days cycle. Not registered in Pakistan; International price for a vial of 1mg is \$1220 approximately, which makes one cycle cost for Eribulin as \$3800 approximately.\*

Ref: Drug Approvals and Databases FDA

## Promising novel second-generation semisynthetic lipoglycopeptides

The emergence of resistance to glycopeptides among Enterococci and Staphylococci has prompted the search for second-generation glycopeptides and semi-synthetic derivatives. Two remarkable agents, Dalbavancin and Oritavancin are on the shelf since 2014. Dalbavancin is the first drug designated as a Qualified Infectious Disease Product (QIDP) to receive FDA approval, whereas Oritavancin is the third one. Oritavancin and Dalbavancin are approved to treat patients with acute bacterial skin and skin structure infections (ABSSSI) caused by certain susceptible bacteria, including *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), various *Streptococcus species* and *Enterococcus faecalis*. Dalbavancin is approved as a two-dose regimen - 1gm I/V once, followed in one week by a dose of 500mg I/V. Oritavancin is used as 1200 mg I/V, single dose. Both drugs can cause red man syndrome as a major side effect. Though not approved for bacteremia, scarce evidence of their use in blood stream infections is present. Dalbavancin costs \$2500 per 500mg vial. Standard 2 dose course of dalbavancin will cost \$7500 approximately while Oritavancin costs \$1500 per 400mg vial approximately. Standard 1200mg single dose therapy will cost \$4500 approximately.\*

Ref: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm408475.htm>

\*Provided cost is approximate and exclusive of import charges