VANCOUVER HOSPITAL & Health Sciences Centre

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In This Issue...

All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical Advisory Council (MAC).

This and other Drug and Therapeutic Newsletters are on the Web at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. Quetiapine 25mg, 100mg, 150mg tablets (Seroquel®)
- Atypical antipsychotic agent for management of schizophrenia
- See page 3 for drug review

2. Zuclopenthixol acetate injection 50mg/mL (Clopixol Acuphase®)
- Intramuscular antipsychotic agent for management of acute psychotic episodes
- See page 4 for drug review

3. Reteplase 2x10U vial kit (r-PA; Retavase®)
- Thrombolytic agent approved for the treatment of acute myocardial infarction
- See page 6 for drug review

Deletions

1. Iron Sorbitol Complex injection (Jectofer®)
- Discontinued by manufacturer
- Alternatives: Iron dextran (Infufer®), Iron sucrose (Venofer®)

2. Hyaluronidase injection (Wydase®)
- Discontinued by manufacturer
- Available through Special Access Programme

3. Penicillin G, benzathine (Bicillin-LA®)
- Discontinued by manufacturer

4. Criticaid®
- Originally brought onto formulary as a skin care product for the treatment of perineal dermatitis resulting from incontinence
- Replaced by ProShield®, a protectant cream, carried by Stores

5. Ticlopidine 250mg tablet (Ticlid®)
- Alternative: Clopidogrel 75mg (Plavix®)

6. Doxapram injection (Dopram®)
- Discontinued by manufacturer

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Updated Policies/Procedures

1. Potassium Chloride Interchange Policy

Effective Monday, Sept 9, 2002, the following interchange policy will take effect:

A. Continuous IV Infusions (1Litre)

Potassium chloride (KCl) doses ≤ 50mEq/L prescribed for continuous infusion in 1 Litre will be interchanged to the nearest 20mEq/L or 40mEq/L solution:

Table 1. Continuous KCl IV Infusions (1 Litre)

KCl Dose Prescribed	KCl Dose Interchange
< 10mEq/L	0 mEq/L
10-30mEq/L	20mEq/L
31-50mEq/L	40mEq/L

This policy will not apply to KCl infusions ordered in volumes less than 1 Litre. Vials will be sent as a personal prescription for all prescribed doses > 50mEq/L.

Premixed KCl bags are available in the following diluents: D5W, D5S, D5-1/2S, 2/3D5-1/3S, NS.

B. Intermittent IV Infusions (50 or 100mL)

KCl doses ordered for intermittent IV infusion in ≤ 100mL diluent will be interchanged to the following premixed minibags in sterile water for injection:

Table 2. Intermittent KCl IV Infusions

KCl Dose Prescribed	KCl Dose Interchange
10-30mEq	20mEq/50-100mL
40mEq	Give 2 x 20mEq pre-mixed minibags

KCl 20mEq in 50mL sterile water for injection is restricted to Critical/Special Care areas for administration by central line only over a minimum of 30 minutes.

KCl 20mEq in 100mL sterile water for injection can be administered on general wards by central line only over a minimum of 60 minutes.

The physician may over-ride both interchange policies by indicating "Do not substitute" after the prescription.

2. Proton Pump Inhibitor Interchange Policy

To streamline the use of proton pump inhibitors (PPI) at VH, pantoprazole will represent the oral PPI and omeprazole MUPS will be administered for nasogastric (NG) use. Table 3 outlines the PPI interchange policy, effective Monday, Sept 9, 2002.

Table 3. Proton Pump Inhibitor (PPI) Interchange Policy

PPI Prescribed	PPI Interchange
ORAL (PO) Esomeprazole (Nexium®) 40mg PO daily Lansoprazole (Prevacid®) 30mg PO daily	Pantoprazole 40mg PO daily
NASOGASTRIC (NG) Pantoprazole 40mg NG daily Esomeprazole 40mg NG daily Lansoprazole 30mg NG daily	Omeprazole MUPS 20mg NG BID

Note that omeprazole MUPS is excluded from this interchange policy and may be ordered for both oral and NG use.

3. Licensed Practical Nurses (LPNs) Medication Administration Policy

LPNs who have successfully completed a formalized pharmacology program authorized by the College of Licensed Nurses of BC (CLPNBC) since the year 2000 and are currently licensed by the CLPNBC may administer medication (including narcotics) to stable adult populations (ie. adult populations whose outcomes are predictable) by all routes other than intravenous and intrathecal. With formal post-basic knowledge and experience, LPNs may administer medications by additional routes in accordance with the agency policy and their competence level.

4. Revised Drug Administration Policies

- **Clopidogrel** (Plavix®) is **no longer** considered a **restricted** drug and may be prescribed by any VH physician.
- **Administration of eptifibatide** (Integrelin®) has been extended to include the **CTU wards (2A, 2C) at the UBCH site**.

New Drug/Drug Products

1. Quetiapine (Seroquel®)

Colette Raymond, Pharm.D.

Pharmacology and Pharmacokinetics

Quetiapine is an atypical antipsychotic with potent serotonin 5-HT_2 receptor antagonism and moderate dopamine D_2 receptor antagonism. Quetiapine also antagonizes serotonin 5-HT 1a, dopamine D_1, histamine H_1, and adrenergic alpha$_1$ and alpha$_2$ receptors. It has no appreciable activity at cholinergic, muscarinic and benzodiazepine receptors.[1] Quetiapine is 100% orally bioavailable and is marginally affected by food. It is extensively metabolized by the liver with the major metabolite produced by the cytochrome P450 3A4 (CYP3A4) isoenzyme. The elimination half-life is 7 hours.[2]

Comparison to Other Antipsychotics

A meta-analysis of several randomized trials of short duration (< 8 weeks) suggests that patients receiving quetiapine were more likely to show improvement in positive and negative psychotic symptoms as compared to placebo (RR 0.798, CI 0.67-0.92, NNT 8).[3] No significant differences were observed between quetiapine and conventional antipsychotics (haloperidol, chlorpromazine) for global state or positive symptoms.[3] A large study (n=255) showed no difference in negative symptoms with quetiapine as compared to haloperidol[4]; however, a smaller study (n=26) did show a small benefit of quetiapine for negative symptoms as compared to haloperidol.[5]

Two indirect comparisons assessed differences between quetiapine and atypical antipsychotics (olanzapine and risperidone).[6,7] Unlike olanzapine and risperidone, quetiapine has not shown to be superior to conventional antipsychotics.[4,7] In a meta-analysis of double-blind, randomized, controlled trials comparing atypical agents to placebo or conventional agents, risperidone was associated with a greater reduction in the Brief Psychiatric Rating Scale compared to placebo than was quetiapine.[6] A second meta-analysis of published, randomized, double-blind, placebo-controlled trials showed that confidence intervals of the calculated effect sizes for each agent versus placebo overlapped.[7] The authors concluded that the atypical agents were not different from each other in terms of acceptability or tolerability.

Dosage and Administration

Quetiapine is initiated at 25mg po BID (with or without food) and gradually titrated up by 25-50mg increments every 2-3 days to a usual maintenance dose of 300-400mg po daily in 2-3 divided doses.[1] The maximum dose is 750 mg/day. For elderly and debilitated populations or patients with hepatic dysfunction, slower dosage escalation and a lower target dose is recommended.[1,2]

Adverse Effects

The most common side effects of quetiapine as compared to placebo are somnolence (18% vs. 11%) and headache (19% vs. 18%).[1] The incidence of extrapyramidal symptoms (EPS), parkinsonism, akathesia and dystonia is similar to placebo and less compared to haloperidol and chlorpromazine.[3-5] There is a trend towards increased dry mouth and sleepiness compared to haloperidol.[3]

Other less frequent adverse effects of quetiapine include orthostatic hypotension (7% vs. 2% placebo), constipation (9% vs. 5% placebo), dry mouth, nausea, vomiting, dyspepsia and asymptomatic increases in liver transaminases.[8] There have been case reports of neuroleptic malignant syndrome, hypothyroidism, neutropenia and asymptomatic QT interval prolongation.[8] Although early animal studies suggested that there was an increase in the incidence of cataracts, no definitive association between quetiapine and cataracts has been established in humans.[8]

Quetiapine has been associated with more weight gain (an increase of 7% from baseline) as compared to placebo (23% vs. 6%) in short-term trials of 3-6 weeks.[1] It does not appear that quetiapine causes more weight gain than olanzapine, but may be greater compared to risperidone.[9]

Drug Interactions

Metabolism of quetiapine is affected by drugs that affect CYP 3A4 . Enzyme-inducers (e.g. phenytoin) may increase the clearance of quetiapine 5-fold; enzyme-inhibitors (e.g. erythromycin, fluconazole) may decrease its clearance. The use of quetiapine with other antipsychotics may cause additive sedation, dizziness, or orthostatic hypotension. Combination therapy with antihypertensives may also cause additive orthostasis. Thioridazine increases the clearance of quetiapine by 65%, requiring upward dosage adjustment of quetiapine.

Cost Comparison

Table 1. Cost Comparison of Formulary Atypical Antipsychotics

Antipysychotic	Usual Daily Dose	VH Acquisition Cost/day
Quetiapine	300mg bid	$7.68
Risperidone	6mg daily	$5.75
Olanzapine	15mg daily	$10.13
Clozapine	300mg daily	$11.33

Role of Quetiapine in Therapy

Quetiapine is an atypical antispychotic that is recommended (along with olanzapine and risperidone) as an alternative for first line therapy of schizophrenia.[10-13] Quetiapine could potentially benefit patients who have experienced EPS with other agents due to its low incidence of EPS. Additionally, quetiapine offers an alternative for patients who have experienced adverse effects or intolerance to other atypical antipsychotics.

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2. Zuclopenthixol Acetate Injection (Clopixol Acuphase®)

Katie Lacaria, B.Sc.(Pharm), Colette Raymond, Pharm.D.

Pharmacology and Pharmacokinetics

Zuclopenthixol is a conventional antipsychotic of the thioxanthene class that has a high affinity for both dopamine D_1 and D_2 receptors, as well as for α_1-adrenergic and serotonin 5-HT_2 receptors. It has low affinity for histamine H_1 receptors, muscarinic, cholinergic and α_2-adrenergic receptors. Zuclopenthixol acetate injection is intended for the initial treatment of acute psychotic episodes or exacerbations of psychosis associated with schizophrenia. Properties of comparable formulary agents are summarized in Table 1.[1] The onset of action of intramuscular (IM) zuclopenthixol is 2-4 hours (15-30 minutes for sedation).[1] Maximal sedation is observed at 8 hours with a prolonged duration of action of 3-4 days.[1] Zuclopenthixol is metabolized by the liver to inactive metabolites.[1]

Table 1. Comparison of Conventional Intramuscular Antipsychotics

Drug	Haloperidol	Loxapine	Zuclopenthixol Acetate
Time to Peak Pharmacologic Effect	30-45 minutes	1.5-3 hours	24-36 hours
Duration of Effect	4-6 hours	12 hours	2-3 days
Usual Dose	2.5-5mg q1-8h	12.5-50mg q4-6h	50-150mg IM q2-3 days
VH Acquisition Cost	$1.65/5mg vial	$4.05/ 50mg vial	$14.98/50mg vial

Comparison to Other Antipsychotics

Zuclopenthixol acetate has been compared with other conventional parenteral antipsychotics (haloperidol, chlorpromazine) for the treatment of acute psychosis in 5 randomized controlled trials.[2-7] The trials were subjected to methodological limitations including high dropout rates and exclusion of patients from final analyses.[2,5,7] Only 3 studies had blinded evaluations of outcomes.[5-7] No differences were observed between zuclopenthixol and any of the conventional antipsychotics in terms of symptom scales, avoidance of additional antipsychotic doses or number of patients leaving the study early. Studies have suggested that

zuclopenthixol acetate produces more intense and earlier sedation. Compared to conventional antipsychotics, more sedation occurred at 2 to 8 hours post-injection[2-4,6]; this was statistically significant in one study at 4 hours, but not at 8 hours post-injection.[6] Reviewers concluded that the literature does not support the use of zuclopenthixol acetate in preference to standard therapy to treat acute psychotic symptoms.[3,4]

The rapid onset and prolonged duration of action of zuclopenthixol acetate theoretically allows for a reduction in the number of times this drug is administered (every 2 to 3 days). A reduction in the number of administrations would lessen a patient's discomfort when oral treatment is unfeasible or unsatisfactory and potentially improve compliance and, hence, treatment conditions.[8] Although the cost of zuclopenthixol acetate is higher than haloperidol, a study indicated that zuclopenthixol acetate may offer a cost savings over haloperidol if it permits a 25% reduction in nursing time to treat agitated patients.[9] There are no studies to date that have compared zuclopenthixol acetate to loxapine, which has shown to have a more acutely sedating effect over injectable haloperidol.[10]

Dosage and Administration

Zuclopenthixol acetate is given as 50-150 mg IM, repeated if necessary every 2-3 days. It should not be used for more than 2 weeks at a maximum cumulative dose of 400mg (maximum 4 injections).[1] Lower doses are recommended in geriatric patients or those with hepatic dysfunction.[1]

Adverse effects

Common side effects with zuclopenthixol acetate include somnolence (16%), hypertonia (25%), tremor (21%), akathesia (16%), dizziness (20%), hypokinesia (21%), dystonia (14%), dry mouth (25%), increased salivation (10%) tachycardia (10%) and visual disturbances (11%).[1] When zuclopenthixol acetate is compared with conventional neuroleptics,[3,4] the incidence of EPS is similar for all drugs except in one study where tremors and akathesia were higher with zuclopenthixol ($p<0.05$).[7] Zuclopenthixol may enhance sedative effects of other central nervous system depressants. Due to the delay in time to peak serum levels as well as the prolonged duration of action, close supervision is needed in order to minimize the risk of over-medication or insufficient suppression of psychotic symptoms.[1,8]

Role of Zuclopenthixol Acetate in Therapy

Zuclopenthixol acetate has shown similar efficacy with a more prolonged duration of action and greater sedative effects compared to conventional antipsychotics used in the treatment of acute psychotic episodes. Zuclopenthixol acetate offers an alternative antipsychotic agent for the management of extremely agitated or aggressive patients where it is anticipated that several days of sedation and symptom management will be required.

Zuclopenthixol acetate should not be used in patients who are antipsychotic-naïve.[11] Its long duration of action may prolong sedation and should therefore be reserved for use in patients with a history of agitation or aggression that required treatment with parenteral medication, seclusion or physical restraint for at least 24 hours.[6]

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3. Reteplase (r-PA)

Deon Druteika, Pharm.D., Rubina Sunderji, Pharm.D., Peter Zed, Pharm.D., Peter Loewen, Pharm.D.

Reteplase (r-PA) is a thrombolytic agent approved for the treatment of acute myocardial infarction (AMI).

Pharmacology

Reteplase, similar to alteplase (t-PA), promotes the conversion of circulating and fibrin-bound plasminogen to the active enzyme, plasmin.[1] The resultant fibrinolysis leads to a dissolution of the coronary thrombus and restoration of coronary perfusion after an AMI.[2] Reteplase is a variant of native tissue-type plasminogen activator. Variations of the native molecule have led to agents with increased fibrin specificity and longer half-life.[2] Due to its longer duration of systemic activity, r-PA is administered as a standard double bolus regimen as opposed to a weight-based bolus and 2-phase infusion protocol with t-PA.[1] As a result, r-PA is more convenient to administer than t-PA.

Comparison with Formulary Thrombolytics

The current formulary thrombolytics at VH are streptokinase (SK) and t-PA. Both agents are indicated in the treatment of AMI but t-PA is also indicated in the acute treatment of stroke.[3] As well, both SK and t-PA may be used for the treatment of acute massive pulmonary embolism, arterial thrombosis and arteriovenous cannula occlusion.

Two comparative trials evaluating the safety and efficacy of r-PA in AMI have been published (Table 1). In order to interpret the results from these trials, the GUSTO-I trial[4], which compared the formulary agents SK and t-PA, is also included. The INJECT[5] trial randomized over 6000 patients with acute MI to receive either SK 1.5 MU or r-PA 10U double bolus (separated by 30 minutes) in conjunction with ASA 75-150mg daily and heparin (5000U bolus followed by 1000U/h adjusted to maintain aPTT 1.5-3 X control). Additional treatments were left up to the discretion of the treating physician. Baseline characteristics were similar in both treatment arms. The primary endpoint of this equivalence trial was 35-day mortality. Statistical evaluation demonstrated that r-PA was at least as effective as SK in reducing mortality. Mortality rates for both treatment arms were higher in comparison to other thrombolytic trials.[4,6] Enrolling patients within 12 hours of symptom onset as opposed to 6 hours, which was an inclusion criteria in the other trials, is one possible explanation for this finding.

GUSTO III,[6] a superiority trial by design, compared r-PA (10U double bolus) to accelerated t-PA in the treatment of AMI. A total of 15 059 patients were enrolled in this trial within 6 hours after onset of symptoms. Adjunctive ASA (160-325mg daily) and heparin (bolus of 5000U followed by 800-1000U/h adjusted to maintain aPTT between 50-70 seconds) were given to all patients. Other medications including beta-adrenergic blockers and nitrates were given at the discretion of the clinician. Baseline characteristics between the two groups were similar. No significant difference was detected in the primary endpoint of 30-day mortality. Therefore, it can be concluded that r-PA is not superior to t-PA, but the results do not imply equivalence of these two therapeutic regimens based on study design.

Table 1. Efficacy Comparison of Formulary Thrombolytic Agents and r-PA

Reference	GUSTO-I[4]	INJECT[5]	GUSTO-III[6]
Population	AMI < 6 h of randomization, median age 62yr	AMI < 12h of randomization, median age 62yr	AMI < 6h of randomization, median age 63yr
Design (n)	R, DB, MC (41,021)	R, DB, MC (6,010)	R, DB, MC (15,059)
Regimen	SK 1.5MU over 1h vs accelerated t-PA*	r-PA 10U double bolus vs SK 1.5MU over 1h	r-PA 10U double bolus vs accelerated t-PA*
Primary Outcome	Mortality at 30 days	Mortality at 35 days	Mortality at 30 days
Results	SK 7.3% vs t-PA 6.3% (p=0.001)	SK 9.53% vs r-PA 9.02% (p=0.0003)**	r-PA 7.47% vs t-PA 7.24% (ns)

AMI= acute myocardial infarction, R=randomized, DB=double-blind, MC=multi-centre, SK=streptokinase, t-PA=alteplase, r-PA=reteplase, ns = not significant

*Accelerated t-PA = 15mg bolus followed by 0.75mg/kg over 30 mins, then 0.5mg/kg infusion over 60 mins (maximum total dose 100mg)

**Based on test for equivalence

Safety

Rates of intracerebral hemorrhage (ICH) and major bleeding were similar between r-PA and t-PA in GUSTO III (Table 2).[6] The ICH rate of r-PA compared to SK in the INJECT trial was approximately two-fold higher, although no p-value was reported.[5] Major bleeding rates and blood transfusions were similar between both thrombolytics in the INJECT trial.

Table 2. Safety Comparison of Formulary Thrombolytic Agents and r-PA

Reference	Regimen	ICH	Major Bleeds*	Blood Trans-fusions
GUSTO-I[4]	SK 1.5MU	0.49%	0.5%	11%
	Accelerated t-PA	0.72% (p<0.003)	0.4%	10%
INJECT[5]	r-PA 10U double bolus	0.77%	4.6%	0.7%
	SK 1.5MU	0.37%	4.7%	1.0%
GUSTO-III[6]	r-PA 10U double bolus	0.91%	0.95%	6.2%
	Accelerated t-PA	0.87%	1.2%	4.25%

ICH = intracerebral hemorrhage; SK = streptokinase, t-PA = alteplase, r-PA = reteplase
*non-intracerebral major bleeds

Other Thrombolytic Agents

Tenecteplase (TNK) is a new variant of t-PA that can be administered as a single weight-based bolus for the treatment of AMI.

The ASSENT-2 trial compared TNK to t-PA in the treatment of 16,949 patients presenting within 6 hours of an AMI.[7] All patients received ASA daily and intravenous heparin adjusted to maintain an aPTT of 50-75 seconds. In this equivalence trial, no difference was detected in the primary endpoint of mortality at 30 days (TNK 6.18% vs t-PA 6.15%). While there was no difference in ICH, TNK was associated with less non-cerebral major bleeding (TNK 4.66% vs t-PA 5.94%, p=0.0002). The clinical significance of this difference is unknown as the impact on morbidity or mortality resulting from the increased bleeding from t-PA was not reported.

Cost

Costs of the thrombolytic agents are listed in Table 3. The cost of r-PA is significantly lower than that of t-PA; however, the manufacturer of t-PA (Hoffmann-La Roche) will reimburse the hospital for any unused portion of t-PA when it is given for AMI or stroke. The acquisition cost of t-PA and TNK are similar; however, once a TNK vial is reconstituted, any unused drug must be discarded after 8 hours. No reimbursement plan for the unused portion of TNK exists.

Table 3. Costs of Formulary Thrombolytics

Drug	Dose for AMI	Cost for AMI
SK	1.5MU	$304.95
t-PA	15mg bolus, 0.75mg/kg x 30 min, then 0.5mg/kg x 60 min (max 100mg)	$2,700.00*
r-PA	10U double bolus 30 minutes apart	$1,900.00
TNK	0.5-0.55mg/kg (max 50mg)	$2,700.00**

*VH acquisition cost based on 70kg patient; partial vials of t-PA are reimbursed by the manufacturer
**based on 70kg patient; TNK not available as a multidose vial so unused portion must be discarded

Role of r-PA

Currently, the standard of practice at VGH is to take all patients presenting with AMI to the catheterization laboratory for percutaneous intervention procedures as opposed to treating them with thrombolytic agents. Individuals who refuse consent or are deemed unsuitable for interventional procedures are considered for thrombolytic therapy with either SK or t-PA. Patients presenting to UBCH with AMI are treated with thrombolytic agents or transferred to VGH for primary angioplasty.

SK is preferred in the elderly due to its lower rate of ICH and is the cost-effective alternative for low-risk AMI. Although r-PA has not been studied for equivalence to t-PA, the mortality rates of r-PA to t-PA were similar in the GUSTO III trial[6] which enrolled over 15,000 patients. The use of r-PA instead of t-PA will enable significant cost savings. Reteplase will be available for use at VGH and UBCH once staff have been educated over the next 1-2 months.

Conclusion

Reteplase is a thrombolytic agent approved for the treatment of AMI. Two large comparative trials of r-PA to SK and t-PA have revealed no differences between the agents in terms of clinical outcomes. Compared to the 3-step accelerated t-PA protocol, r-PA provides a more convenient double bolus (non-weight-based) regimen. This simplified r-PA regimen may result in less medication errors and reduced time to treatment of an AMI. The acquisition cost of r-PA is also considerably less than t-PA.

Currently, both t-PA and SK will be retained on formulary. Alteplase has a unique indication for the acute treatment of stroke and SK is preferred in the elderly and is the cost-effective alternative for low-risk AMI.

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Iron Sucrose (Venofer®): Serious Adverse Events at VH

Karen Shalansky, Pharm.D., B.Benny, MD, Hematology

There have recently been 2 cases of anaphylactoid-type reactions at VGH following the administration of the first dose of iron sucrose. In both cases, the iron sucrose dose given was greater than the maximum recommended dose of 500mg. In the first case, 1000mg was ordered over 6 hours and anaphylaxis occurred at hour 3. In the second case, 800mg of iron sucrose was ordered over 6 hours and the reaction occurred at hour 4. In addition, a third reported case of hypotension and back pain occurred 3.5 hours into the infusion of the first dose of iron sucrose 500mg over 3 hours. In all cases, the rate of the iron infusion at the time of the reaction occurred was ≥ 150mg/hour. The authors are also aware of 2 further cases of urticaria and joint pain (dose/rate unknown). Although the majority of literature on iron sucrose deals with renal dialysis patients and doses of 100mg per dialysis session, there is some literature on higher doses suggesting that, similar to iron dextran, adverse events are rate-related (and possibly dose-related).[1,2]

Due to the serious nature of these adverse events, the monograph for iron sucrose in the VH Parenteral Drug Therapy Manual (PDTM) will be amended to state that a **MAXIMUM SINGLE DOSE of iron sucrose of 500mg** must be administered at a **MAXIMUM INFUSION RATE of 100mg/hour**. Physicians will be contacted if higher than these maximums are prescribed.

Since anaphylactoid reactions and hypotension may occur with intravenous iron preparations, epinephrine and an antihistamine must be readily available.

Please note that the maximum dose of iron dextran injection to be given at VH has also been capped at 1000mg due to recent guidelines.

Please feel free to contact Dr. Benny, Hematology or Dr. Karen Shalansky (875-4839) for further clarification.

References

1. Chandler G et al. Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis 2001;38:988-91.
2. Van Wyck DB et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. Amer J Kid Dis 2000;36:88-97.