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

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Changes to Formulary

Additions

- 1. Citalopram tablets (Celexa®)**
 - Selective serotonin reuptake inhibitor (SSRI) antidepressant
 - See page 3 for review
- 2. Oxycodone tablets (Supeudol®)**
 - Semi-synthetic opioid for relief of moderate to severe pain
 - See page 5 for review
- 3. Pantoprazole 40mg IV (Pantoloc-IV®)**
 - Parenteral proton pump inhibitor restricted for the initial management of acute upper gastrointestinal bleeding and for patients who are unable to tolerate oral medication
 - See page 6 for review

Deletions

The following products have been discontinued by the manufacturer:

- 1. Dimetapp® tablet and elixir**
 - Products with phenylpropanolamine have been removed from the market
 - Alternative: Actifed®
- 2. Neomycin tablets, solution (Mycifradin®)**
- 3. Procarbazine 50mg capsules (Natulan®)**
- 4. Bonney's Blue Solution**
- 5. Sulfadiazine 500mg tablets**
- 6. Antivert® tablets**
 - Alternative: meclizine 25mg (Bonamine®)
- 7. Anileridine tablets, injection (Leritine®)**
 - Alternatives: oxycodone, morphine, hydro-morphone
- 8. Savlon® Solution**
 - Alternative: chlorhexidine 0.05% solution
- 9. ACTH injection**
 - Alternative: cosyntropin injection

EDITORIAL STAFF:

Karen Shalansky, Pharm.D., FCSHP

Peter Loewen, Pharm.D.

Rubina Sunderji, Pharm.D., FCSHP

Peter Jewesson, Ph.D., FCSHP

Any comments, questions or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email kshalans@vanhosp.bc.ca Find us on the Web at www.vhpharmsci.com

Updated Policies/Procedures

1. CMI Multitest® Interchange to Candida plus Mumps Skin Tests

CMI Multitest® is no longer available on the market. As a result, an automatic substitution policy has been implemented whereby all orders for CMI Multitest® will be interchanged to candida plus mumps skin tests. The skin tests are administered intradermally using the Mantoux technique (see patient care guidelines T-300).

2. Sublingual Sufentanil

Dr. W. Yeomans, Dr. DHS Hsu, Karen Shalansky, Pharm.D.

The sublingual administration of sufentanil has been approved for the management of incident pain in select palliative patients.

Background

The management of incident pain (ie. pain with movement or procedural pain) is difficult because of its rapid onset, intensity, and transient nature. Oral analgesics often do not have a fast enough onset of action and frequently outlast the pain, creating unwanted side effects such as excessive sedation, nausea and confusion. In addition, many of these patients have no intravenous access and are otherwise well controlled on oral analgesics.

The ideal medication for incident pain should be rapidly absorbed, have a fast onset to effect time, have a short duration of action, and be highly effective with tolerable adverse effects. The sublingual route of administration offers a highly vascular space which avoids first pass metabolism, thereby increasing absorption rate and bioavailability compared to the oral route.

Other Narcotics

Morphine, a hydrophilic drug, remains predominantly ionized at the physiological pH of the mouth and is poorly absorbed sublingually (~18%). In contrast, the opioid analgesic, fentanyl, a highly lipophilic drug, is absorbed sublingually to a much greater extent (~30-50%). The limitation with fentanyl is that it is only available as a 50mcg/mL solution and volumes in excess of 1mL are difficult to deliver via the sublingual route. As starting fentanyl doses are in the range of 50-75mcg (1-1.5mL), the opioid tolerant patient would virtually be excluded from receiving any benefit from fen-

tanyl due to its low potency per volume.

Sufentanil

Sufentanil belongs to the same class of opioids as fentanyl. Sufentanil is approximately ten times as potent per volume than fentanyl, thus allowing smaller volumes less than 1mL to be given sublingually. A recent open-label pilot study at UBC Hospital found sublingual sufentanil to be effective and well tolerated for this indication.

Pharmacokinetics and Dosage

The onset of analgesic action for sublingual sufentanil occurs within 3-5 minutes. Duration of analgesic action is approximately 10-25 minutes. Because of incomplete and variable cross-tolerance along with significant individual variation, there is no known consistent equivalent dose ratio to calculate when using sufentanil for incident pain. Therefore, incremental titration is required for each patient. The usual dose range is 5-25mcg (0.1-0.5mL) sublingual pre-procedure; the maximum dose is 50mcg (1mL) per episode. One hour should elapse before giving sufentanil for the next procedure. The patient should be instructed to not swallow for 2 minutes. Three to five minutes should elapse before attempting the procedure.

Side Effects and Monitoring

Side effects may include drowsiness, hypotension, dizziness, hypertension, chest wall rigidity and bradycardia. Respiratory depression may occur but is highly unlikely in doses used sublingually. Sedation scale and respiratory rate should be monitored every 5-10 minutes for 25 minutes after each dose.

A drug data sheet for sublingual sufentanil is available from CSU Pharmaceutical Sciences.

3. Revised Drug Administration Policies

- **Quadruple strength norepinephrine (16mg/250mL D5W or D5S)** has been approved for administration in special and critical care areas. Administration flowsheets are available from Pharmacy upon request.
- **Ketamine** may be administered **IM by nurses in critical care areas** if the anesthetist (or any physician) is present.
- **Dopamine** has been approved for administration at **rates > 5mcg/kg/min** in **SICU** as well as critical care areas and NICU.

- **Labetalol** may be administered at concentrations of **200mg/250mL (0.8mg/mL), 200mg/200mL (1mg/mL) and 200mg/100mL (2mg/mL)**. Administration flowsheets are available from Pharmacy upon request.
- **Fentanyl** may be administered by **SC infusion** in the **Palliative Care Unit**.
- **Alteplase**, when used for **intracannular infusion by radiology** for lysis of acute occlusion of an artery, vein, catheter or graft, will be administered at a concentration of **12.5mg/500mL NS** infused at a rate of **0.5-2.0mg/hour** (usual 1mg/hour) x **6-72 hours**.
- The **new ACLS dosing guidelines for amiodarone** have been inserted into all patient care unit PDTMs. Amiodarone has also been added to all crash carts.

4. Morphine Interchangeability

Morphine tablets and elixir are considered interchangeable at VHHSC. A physician's order is not required for this interchange.

MS Contin® and M-Eslon® are two brands of extended release morphine. Both brands are considered interchangeable at VHHSC. CSU Pharmaceutical Sciences currently carries M-Eslon®, a capsule which may be opened, if necessary, and the beads mixed with soft food, liquid or given by gastric tube. To prevent any confusion between these two extended release products, the label that will appear on the MAR for an order for MS-Contin® 15mg (for example) is as follows:

- Morphine 15mg cap Ext.Rel. (M-Eslon) (equivalent to MS-Contin)

New Drug/Drug Products

1. Citalopram (Celexa®)

Adele Runikis, B.Sc.(Pharm), Peter Loewen, Pharm.D.
Reviewed by Dr. R. Raina, Psychiatry

Pharmacology & Pharmacokinetics

Citalopram is a highly selective serotonin reuptake inhibitor (SSRI) which selectively blocks presynaptic reuptake of serotonin in the brain with little effect on dopamine and noradrenaline. It has little or no activity at muscarinic, cholinergic, adrenergic, hista-

minergic, serotonergic, or dopaminergic receptors. Citalopram is > 80% orally bioavailable and is unaffected by food. It is metabolized by cytochrome P450 enzymes and is a weak inhibitor of the 2C19, 3A4, and 2D6 isoenzymes. The elimination half-life is 30-35 hours.

Indication and Efficacy

Citalopram is indicated for the treatment of depression. Onset of antidepressant activity occurs within 3 weeks and is maximal after 6 weeks¹, which is similar to most other SSRIs. Fluoxetine is an exception with a slower onset of action.²

In randomized placebo-controlled trials using doses of 10-80 mg/day, citalopram was significantly more effective than placebo when assessed using the HDRS, CGI, Zung, and MADRS depression measurement tools.³ A meta-analysis of 5 placebo-controlled trials involving 396 patients found that the proportion of patients with a ≥ 50% reduction in HDRS was 15% (intention-to-treat analysis) or 18% (efficacy analysis) higher with citalopram than with placebo (p<0.05).⁴ A recent large placebo-controlled trial (N=650) has confirmed this result.⁵ Citalopram is more effective than placebo in treating post-stroke depression over 6 weeks.⁶

Four randomized, controlled head-to-head comparisons with other SSRIs have been published. At 8 weeks, citalopram 20mg was equally efficacious to fluoxetine 20mg.⁷ Another fluoxetine vs. citalopram trial showed similar efficacy but severely depressed patients responded better to citalopram.⁸ In an unblinded 6-week trial, 30-40mg citalopram (mean dose 38mg) was similarly effective to fluvoxamine 150-200mg (mean dose 191mg).⁹ Sertraline 50-150mg and citalopram 20-60mg were equally effective when evaluated at 24 weeks.¹⁰ A meta-analysis of 20 comparative SSRI trials revealed no significant differences in efficacy between any SSRIs, including citalopram.² Randomized controlled comparisons between citalopram and amitriptyline, clomipramine, and imipramine have consistently produced equivalent efficacy results after 6 weeks of treatment.³

No controlled trials of citalopram alone in treatment-refractory patients have been published, although it is accepted that patients may respond differently to different SSRI agents. Augmentation of the antidepressant effects of citalopram by adding lithium¹¹ or fluvoxamine¹² has been evaluated with some success.

Dosage and Administration

The usual dosage range for citalopram is 20 to 60mg orally once daily. Lower initial doses (10mg) may be used in elderly patients and patients with hepatic impairment. Lower maximum doses (40mg) should be used in these patients as well. The initial dose of 20mg daily may be increased by 20mg at intervals of at least one week, to a maximum daily dose of 60 mg. A linear dose-response relationship from 20-60 mg/day appears to be present.^{2,13}

Adverse Effects

The most common adverse effects (at 20-40mg/day) are similar to other SSRIs and include dry mouth (19-28%), sweating (20%), nausea (19%), insomnia (18%), tremor (15%), headache (15%), somnolence (14%), constipation (13%), asthenia (12%), dizziness (9%), ocular accommodation disorders (9%), diarrhea (7%), agitation (6%) and sexual dysfunction (ejaculatory delay, anorgasmia, impotence, reduced libido) (5%)^{2,14,16} A meta-analysis of trials comparing citalopram to fluoxetine, fluvoxamine and sertraline revealed no differences between the drugs in adverse effect profiles.² Citalopram is better tolerated than tricyclic antidepressants with respect to anticholinergic side effects.³ No serious adverse events have been associated with citalopram to date.

Like other SSRIs, citalopram is relatively safe in overdose due to its relative freedom of cardiotoxic effects. It is speculated that citalopram may be more lethal in overdose situations than other SSRIs, although this is based on only six successful suicides, five of which co-ingested other substances.¹⁶

Drug Interactions

Citalopram's relative lack of cytochrome P450 effects confers a lower risk of clinically significant drug-drug interactions compared to other SSRIs (eg. fluoxetine, fluvoxamine, paroxetine).² Lack of effect on the pharmacokinetics/dynamics of haloperidol, chlorpromazine, zuclopenthixol, methotrimeprazine, thioridazine, perphenazine, maprotiline, imipramine, clozapine, digoxin, carbamazepine, and warfarin has been confirmed in controlled studies.^{15,17} Citalopram serum concentrations are increased by cimetidine, fluvoxamine and clomipramine, although the clinical relevance of this is not known.¹⁷ Serotonin syndrome has been reported when citalopram was

combined with either buspirone or dexfenfluramine.¹⁵ Although there is an apparent advantage over most SSRIs, citalopram and sertraline are comparable in their drug interaction profiles.

Relative Cost

SSRI	Usual Daily Dose (mg)	Daily Cost ^a
Sertraline	50	\$1.48
Paroxetine	20	\$1.59
Fluoxetine	20	\$0.57
Fluvoxamine	100	\$1.48
Citalopram	20	\$1.25
	40	\$1.25
	20 (half scored 40mg tab)	\$0.63

^abased on VHHSC acquisition costs

Conclusions

Citalopram is an SSRI which may be useful in patients who do not respond to other SSRIs or in whom drug interactions are a concern. It does not appear to have significant efficacy advantages over other SSRIs or an improved tolerability profile. However, it is recognized that some patients who do not respond to one SSRI may respond to another, and for this reason it has been added to the armamentarium of antidepressants available for use at VHHSC.

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2. Oxycodone (Supeudol®)

Karen Shalansky, Pharm.D.

Oxycodone is a semi-synthetic opioid which has a basic chemical structure similar to morphine. Oxycodone is indicated for the relief of moderate to severe pain. It differs from morphine in that it does not contain a 6-hydroxyl group, resulting in a potential for less cross-reactivity to morphine or other congeners. However, caution should be exercised for true anaphylactic reactions.¹ In addition, oxycodone does not have a 3-glucuronide metabolite as does morphine. This metabolite has been associated with hallucinations and delirium.² In comparative trials, hallucinations reported with morphine have not been reported with oxycodone.^{3,4} As with morphine, oxycodone is partially metabolized to noroxycodone. In general, accumulation of nor-metabolites may pro-

duce central hyperexcitability.²

Since the removal of anileridine (Leritine®) from the market, the oral straight narcotic formulary alternatives to morphine include codeine, hydromorphone and oxycodone. Codeine is considered a weak narcotic indicated for mild-moderate pain, and may display unwanted side effects if administered in high doses necessary for morphine equivalence. Hydromorphone is a high potency narcotic which also contains a 3-glucuronide metabolite. Table 1 provides a comparison of some features of formulary oral narcotics at VHHSC.

Conclusion

Oxycodone represents a less expensive alternative to anileridine, which has been recently removed from the Canadian market. It is structurally related to morphine with a lower likelihood of cross-reactivity and possibly a lower incidence of hallucinatory side effects.

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Table 1. Comparison of Oral Formulary Narcotics

Narcotic	6-hydroxyl group	3-glucuronide group	Nor-Metabolite	Oral Dose Equivalence	Cost/dose Equivalence ^a
Morphine	Yes	Yes	Yes	20-30mg	\$0.22-0.33
Hydromorphone	No	Yes	?	4mg	\$0.12
Codeine	Yes	Yes	Yes	200mg	\$0.35
Oxycodone	No	No	Yes	15-20mg	\$0.54-0.70
Anileridine	Not morphine structure	-	Yes (normeperidine)	75mg	\$1.02

^abased on VHHSC acquisition costs

3. The Role of IV Pantoprazole (Pantoloc® IV)

Peter Zed, Pharm.D.

Introduction

Proton pump inhibitors (PPI) have proven to be the most potent antisecretory agents available on the market today; however, until recently no parenteral formulation was available in Canada. The first intravenous (IV) formulation, pantoprazole, was marketed for rapid acid-suppression in patients unable to tolerate oral agents. This review will outline the role of pantoprazole IV at VHHSC.

Pharmacology/Pharmacokinetics

Pantoprazole, as do all PPI, inhibits the final stage in gastric acid secretion through covalent binding and inhibition of the H⁺/K⁺/ATPase pump of the gastric parietal cell. It is a weak base that must be converted to the active form by gastric acid before acting on the proton pump.¹

Pantoprazole is extensively metabolized in the liver to inactive metabolites. It has a plasma half-life of 1.1 hours but antisecretory effects persist for up to 24 hours due to the covalent binding of the active drug to the proton pump.^{2,3}

Intravenous pantoprazole results in immediate acid suppression. Various dosage regimens have been evaluated and trials comparing IV pantoprazole 40 mg with oral pantoprazole 40 mg have demonstrated that each route of administration produces similar effects on acid output. A dose of 40 mg orally produces a median intragastric pH of 3.1 compared to 3.3 when administered IV in healthy adults.⁴ In a study conducted in patients with gastroesophageal reflux disease (GERD), oral doses of pantoprazole 20 or 40 mg produced the same effect on maximal acid output as did the same doses administered IV bolus.⁵

As a higher intragastric pH is ideal for management of acute gastrointestinal (GI) bleeding, various continuous infusion regimens have been evaluated.⁶⁻⁸ Administration of a single bolus of 80mg followed by a continuous infusion of 8mg/hr resulted in maintenance of intragastric pH > 6 for more than 80% of the day which was superior to various comparative regimens of continuous infusion and intermittent bolus dosing of PPI and H₂ receptor antagonists (H₂RA) (e.g. ranitidine).^{7,8}

Clinical Use

The approved indications for IV pantoprazole are conditions where rapid reduction of gastric acid

secretion is required in hospitalized patients unable to take oral or nasogastric (NG) PPI. In addition, there is evidence for use in patients with acute upper GI bleeding peptic ulcers.

Acute upper GI bleeding peptic ulcers occur with a prevalence of approximately 100 cases per 100,000 adults per year and account for about 150 hospitalizations per 100,000 patients.^{9,10} Despite advances in diagnostics and surgical techniques, mortality remains at 10-15%. While bleeding stops spontaneously in 80% of patients, further intervention is required in the remaining 20% and it is in this group where studies have focused on evaluating antisecretory therapy as a means to reduce morbidity and mortality. Although clinical correlates have attempted to risk stratify patients with upper GI bleeding ulcers, endoscopic findings have proven to be more valuable in stratification of patient risk. Endoscopic findings of active bleeding, a non-bleeding visible vessel or a clot all indicate high risk potential which persists for up to 72 hours following the onset of the bleed.^{9,10}

Early trials of antisecretory therapy for acute upper GI bleeding evaluated the use of H₂RA. A meta-analysis performed in 1985 suggested a benefit with H₂RA for upper GI bleeds.¹¹ However, a more recent randomized, double-blind, placebo-controlled trial in 1,005 patients with high risk endoscopic findings found that famotidine infusion x 72 hours offered no advantage compared to placebo in the prevention of rebleeding, need for surgery or mortality.¹² Based on this study, it was concluded that H₂RA have no role in the management of acute upper GI bleeding.

To date, there have been nine studies published in english evaluating the role of PPI in acute upper GI bleeding, all involving IV omeprazole.¹³⁻²¹ Early trials assessed the role of intermittent bolus dosing of 40mg IV every 8-12 hours compared to either placebo or H₂RA.¹³⁻¹⁷ In general, very little benefit was observed in any of these trials and thus intermittent bolus dosing of PPIs appear to have no role in the management of this condition. Recent trials evaluating continuous infusion of IV omeprazole have indicated promising results.¹⁸⁻²¹ Hasselgren et al conducted a prospective, randomized, double-blind, placebo-controlled trial using omeprazole 80 mg IV bolus followed by 8 mg/h for 3 days in endoscopically proven, high-risk upper GI bleeding. The authors found that omeprazole reduced the rebleeding rate (8.2% vs. 17.4%, p=0.004) and need for surgery (2.5% vs. 9.8%,

$p=0.003$) but had no impact on mortality.¹⁸ A similar trial that randomized high-risk patients following endoscopic therapy also demonstrated that IV omeprazole reduced rebleeding rate (18% vs. 31.4%, $p=0.03$) and need for surgery (5.4% vs. 11.1%, $p=0.04$) but again had no impact on mortality.¹⁹ The most recent trial by Lau et al randomized 240 high-risk patients with upper GI bleeds following endoscopic therapy to receive omeprazole 80 mg IV bolus followed by 8 mg/hr or placebo for 3 days and again demonstrated a reduced rebleeding rate (4.2% vs. 20.0%, $p<0.001$) but no impact on need for surgery or mortality.²¹

A recent meta-analysis of the 9 English-language trials involving a total 1,829 patients demonstrated a 50% reduction in the odds of rebleeding in the PPI-treated group (95% CI 0.33-0.77, $p=0.002$, NNT = 9).²² The relative odds of surgery indicated a 53% reduction in the PPI-treated group (95% CI, 0.29-0.77, $p=0.003$, NNT = 17). There was a non-significant 8% decrease in the relative odds for mortality in the PPI-treated group. Subgroup analysis demonstrated significant results only when omeprazole was administered by continuous infusion, not by intermittent bolus. As IV omeprazole is not marketed in Canada, IV pantoprazole is the only agent available for use.

Adverse Effects

Intravenous pantoprazole is well tolerated with the most common adverse effects being headache (0.7%) and diarrhea (0.3%). Other less common adverse effects include thrombophlebitis at the site of injection and other GI effects such as flatulence, nausea and cramps.¹⁻³

Drug Interactions

Azole antifungal agents (ketoconazole and itraconazole) require an acidic intragastric pH for absorption. Reduced bioavailabilities have been observed when co-administered with H₂RA and PPI. Due to the potential for antifungal failure, the combination of PPI and azoles should be avoided.¹⁻³

Dose and Cost

The usual IV dose of pantoprazole is 40mg daily for patients unable to tolerate oral therapy. For management of acute upper GI bleeding, an 80mg IV bolus is followed by an 8mg/hour continuous infusion for 72 hours. Intermittent bolus dosing is of no benefit in these patients. The acquisition cost of pantoprazole 40mg IV daily is \$13.70/day. For the management of acute upper GI bleeding, the total 72-hour cost is ~\$220.00.

Conclusions

Pantoprazole IV offers an advantage for patients unable to tolerate oral/NG PPI therapy and for patients requiring antisecretory therapy following acute upper GI bleeding peptic ulcers. Omeprazole still remains on our formulary oral PPI.

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Adverse Drug Reaction Report 2000

There were a total of 34 suspected adverse drug reactions (ADRs) reported at VHHSC in 2000 (Table 1). Of note, 19 reactions were considered to have been the cause of hospitalization, 4 resulted in prolonged hospitalization and 1 ADR resulted in death. The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in an improved assessment of the magnitude and nature of adverse events. To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to Pharmaceutical Sciences CSU, or call local 62481 (VGH site) or local 27249 (UBC site). Pharmacists complete all ADR report forms and forward copies to the B.C. Regional ADR Centre. This Centre does preliminary analysis of the data and then forwards all reports to the Canadian ADR program in Ottawa who then forward them to the World Health Organization.

Table 1. Adverse Drug Reactions Reported in 2000

Drug	Suspected ADR	Drug	Suspected ADR
Alendronate	Mild esophagitis on endoscopy (1)	Imipenem, Ciprofloxacin, Cloxacillin, Fluconazole, Clindamycin, Acyclovir	Diffuse maculopapular rash, skin biopsy suggestive of erythema multiforme (1) ^b
Allergy Injection: Dust Mite, Alder Birch, Grass	Facial swelling (1) ^a	Iodine Contrast Dye	Generalized pruritic rash (1)
Amoxicillin	Neutropenia, maculopapular rash (1) ^a	Iron Dextran Injection (third dose)	Facial flushing, throat tightening, hypotension (1) ^a
Bupropion SR (Zyban®)	Erythematous, urticarial rash, facial/lip swelling, periorbital edema (1) ^a	Metformin	Lactic acidosis (1) ^a
Celecoxib	Upper GI bleed (1) ^a ; Maculopapular, pruritic rash (1) ^a	Methimazole	Agranulocytosis (1) ^a
Ciprofloxacin	Diffuse pruritic rash (1)	N-acetylcysteine	Anaphylactoid reaction (1) ^b
Ciprofloxacin plus Tamsulosin	Periorbital/throat/hand swelling, and rash (1)	Naproxen plus Levofloxacin	Pulmonary infiltrates, eosinophilia (1) ^a
Ciprofloxacin plus Warfarin	Hemoptysis, epistaxis, "bloodshot" eyes (1) ^a	Phenytoin	Facial complex tics (1)
Clopidogrel plus Cotrimoxazole	Severe arthralgias and high fever (1) ^a	Propofol	Acute dystonia (violent jerking of all limbs (1)
Clopidogrel plus Ramipril	Erythema multiforme vs. drug-induced urticarial vasculitis (1) ^a	Ramipril	Tongue/lip swelling (1) ^a
Cotrimoxazole	Generalized maculopapular rash, fever (1) ^a ; pancytopenia (1) ^b	Rofecoxib	Vomiting and hematemesis (1); SOB and pulmonary edema (1) ^a
Dapsone	Methemoglobinemia (1) ^a	Spirolactone	Maculopapular, pruritic rash (1)
Edrophonium	Non-cardiogenic pulmonary edema ^a	Valsartan	Hyperkalemia (1) ^a
Etidronate/Calcium (Didrocal®)	Neutropenia, decreased platelets & hemoglobin (1)	Vancomycin	Acute interstitial nephritis, eosinophilia, pancytopenia, rash, fever (1) ^b ; increased serum creatinine (1)
Ganmaoling (Herba Menthae, Chrysanthemum, Lonicerae)	Increased serum creatinine (biopsy proven nephritis, non-specific), increased LFTs (1) ^a	Warfarin	Intracranial bleed (1) ^c (pt had fallen, INR 9.2 at time of fall)

^ahospitalized due to ADR ; ^b prolonged hospitalization due to ADR; ^cdeath due to ADR