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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 18, 2005. 1 drug was added in the *Formulary* and no drugs were deleted. 1 drug was evaluated and not added.

◆ **ADDED**

Glimepiride
(Amaryl® by Aventis)

◆ **DELETED**

None

◆ **EVALUATED, BUT NOT ADDED**

Dexmedetomidine
(Precedex® by Hospira)

Glimepiride is a second-generation sulfonylurea with labeled indications for the treatment of type 2 diabetes as monotherapy and in combination with metformin or insulin. It was evaluated because of high volume nonformulary use.

All sulfonylureas are thought to work by stimulating the release of insulin from functioning beta cells. Adverse events associated with sulfonylureas are hypoglycemia, hyponatremia, and disulfiram-like reactions. Hypoglycemia is the most common adverse event associated with glimepiride.

There are 2 randomized trials comparing glimepiride and glyburide. No differences in efficacy were detected in these studies. When comparing adverse events, 1 study showed no significant difference in the number of hypoglycemic events and another showed a significant difference during the first month of treatment, but no difference over the rest of the study period.

Glimepiride is roughly 3 times more expensive than glyburide. However, the patent for Amaryl® expires in April 2005, and the FDA has

(continued on next page)

MEDICATION SAFETY

Avoiding "greater than" and "less than" abbreviations

As reported last month, eliminating banned abbreviations continues to be a focus at Shands at UF. Some improvement has occurred and current compliance is between 60–70%. The Academic Quality Support Agreement (AQSA) target is 90%; therefore, efforts continue to decrease the use of the banned abbreviations (see table on page 3).

Efforts continue to decrease the use of the banned abbreviations. The AQSA target is 90% compliance.

The greater than (>) and less than (<) symbols are more than 60% of the banned abbreviations being used. These symbols are listed as error-prone abbreviations by the Institute for Safe Medication Practices because they may be mistaken for numerals (eg, ">" as 7, or "<10" as 40) and are easy to invert (ie, mean less than, but use the abbreviation for more than). By avoiding these abbreviations, errors can be avoided.

A recommended method of avoiding writing "greater than" and "less than" repeatedly is the use of columns. The figure above shows a method that uses "greater than" and "less than" columns with several monitoring parameters specified.

Unfortunately, other unsafe alternatives to ">" and "<" have been noticed. Use of up and down arrows (ie, ↑↓) and the plus symbol (ie, +) do not result in clear orders. These are not banned abbreviations, at least not yet. However, it is best to spell out "greater than" or "less than." The use of columns may save some time.

Another problem we have noticed while auditing charts for banned abbreviations is the use of ditto marks (“). For example, in order to avoid writing "units" several times in a sliding scale insulin order, the prescriber will write out "units" in the first line, then use ditto marks in each row below. Ditto marks could be misread as numbers, leading to incorrect doses of insulin. Please avoid the use of dittos when writing orders.

Arrows, plus signs, and ditto marks are not explicitly banned symbols, but they contradict the intent of the Joint Commission's rules, which are intended to decrease medication errors.

ALTERNATIVE TO GREATER THAN AND LESS THAN SYMBOLS

Call house officer if:	*Less than*	*Greater than*
TEMP	N/A	38.3 C
HR	60	110
BP Systolic	100	180
RR	10	30
O_2 Sat	92%	N/A

INSIDE THIS ISSUE

Formulary, *from page 1*
already tentatively approved generic equivalents for Amaryl®. The cost of glimepiride should drop considerably by the end of 2005.

Therapeutic interchange with glipizide or glyburide was considered. However, the P&T Committee felt that this might increase the possibility for medication errors in the outpatient setting. For example, a prescription for the interchanged drug (eg, glipizide) could be written at discharge and taken with the patient's home prescription for glimepiride. This could result in hypoglycemia.

Another medication safety issue related to glimepiride is the sound-alike problem with the brand name Amaryl® and Reminyl® (galantamine), a drug used to treat Alzheimer's disease. Although both drugs share a common dosage strength (ie, 4 mg), Amaryl® is given once daily and Reminyl® is given twice a day. There have been reports of patients getting Amaryl® instead of Reminyl® leading to episodes of hypoglycemia. This could be life-threatening.

Patients receiving Reminyl® instead of Amaryl® could experience hyperglycemia. Cholinergic adverse effects like nausea, vomiting, and diarrhea may also occur if patients take Reminyl® instead of Amaryl®.

Name confusion with these drugs is particularly a problem with verbal orders. Prescribers and other health care providers (eg, nurses and pharmacists), should spell verbal orders for these agents and specify why the drug is being given (eg, Amaryl® 4 mg daily for diabetes). The use of generic names is also recommended. Although the dosage frequency should be instructive, relying on this information alone is insufficient. There are news reports that Aventis is considering changing the brand name of Amaryl®.

Dexmedetomidine is a relatively selective alpha$_2$-adrenoreceptor agonist with sedative properties. It has a labeled indication for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. The labeling states that treatment should not exceed 24 hours; however, it is used for longer durations according to published reports.

The FDA approved dexmedetomidine for marketing in 1999. The P&T Committee initially reviewed dexmedetomidine in May of 2002. At that time, the Committee determined that there was insufficient evidence to support its addition in the *Formulary*, and it was designated nonformulary and not available.

Dexmedetomidine was re-evaluated for use in several patient populations. A purported advantage is that it does not need to be stopped in order to do a neurological exam like propofol. This could allow for a more cooperative patient, yet allow assessment of neurological function. Also, patients experiencing alcohol withdrawal syndrome may benefit from its sympatholytic effect. Another possible niche would be as a sedative in non-intubated patients for short procedures. This could eliminate the need for an anesthesiologist, which is required when propofol is used.

It was also discussed that young patients may develop "propofol infusion syndrome." Having dexmedetomidine may have offered an alternative for these patients.

The cost of dexmedetomidine was also considered. Dexmedetomidine continues to be roughly 5-times more expensive that propofol. Assuming average doses and a duration of 3 days per patient, 50 patients per month would increase annual pharmaceutical expenditures by approximately $850,000 per year. If dexmedetomidine is used in more patients, expenditures would easily increase by more than $1 million.

Current benchmarking data suggest dexmedetomidine is not widely used in teaching hospitals. The lack of published outcome data and the high cost are likely factors. The P&T Committee considered the current published evidence and concluded that there is still insufficient evidence to add dexmedetomidine in the *Formulary.*

NEWS

New drugs in 2004

Reversing the trend of the last few years, the number of new drugs approved by the FDA increased in 2004 (see table on page 4). Several new drugs were approved at the end of the year including 4 in December. This year-end rush occurred despite concerns that the removal of rofecoxib (Vioxx®) from the market would decrease drug approvals because of increased safety concerns. Nearly 50% of the new drugs approved in 2004 came after the September 30th Vioxx® withdrawal. However, the number of new drug approvals is expected to decrease in 2005 because of increased safety concerns.

Several important new biologicals were approved in 2004. This continues the trend of increasing biological approvals. The table includes some of the significant new biologicals that were approved in 2004.

Drugs used to treat cancer led approvals with 6 new products, including 2 new monoclonal antibodies (bevacizumab and cetuximab). There were 3 new drugs approved for overactive bladder and 2 new drugs for pain. There were no other notable trends in the type of new drugs approved last year. Many of the new products were developed by small companies.

◆

Next year should continue the trend of increasing approvals of important new generic drugs.

2004 was another big year for first-time generic approvals. Generic versions of blockbuster drugs continue to be marketed as patents expire. Several generic anti-infective products were approved. Generic antibiotics (eg, amoxicillin-clavulanate, ciprofloxacin, clarithromycin, levofloxacin, piperacillin), antivirals (didanosine and ribavirin), and antifungals (fluconazole and itraconazole) can now be marketed.

Several new cardiovascular generic drugs were also approved. Most ACE inhibitors are available as generics, now including benazepril, fosinopril, and quinapril. Other cardiovascular generics that were approved include adenosine injection, esmolol injection, and felodipine.

Generic antidepressants (eg, bupropion ER, citalopram, mirtazepine) and cancer agents (eg, carboplatin, dexrazoxane, fludarabine) were also approved. Generic versions of cilostazol (Pletal®), flumazenil (Romazicon®), gabapentin (Neurontin®), and polyethylene glycol 3350 (MiraLax®) should eventually result in lower costs for these agents.

Next year should continue the trend of increasing approvals of important new generic drugs. The FDA is struggling, however, with the best method of approving generic biological agents.

The ins & outs of continuous infusion diuretics

The use of continuous infusion (CI) diuretics offers several advantages over traditional bolus dosing. These include production of a more consistent urine flow, fewer alterations in fluid balance and electrolytes, as well as utilization of a lower dose of diuretic. It has also been proposed that the use of a CI may result in less toxicity due to the avoidance of high peak serum concentrations. Continuous infusion loop diuretics have been studied in congestive heart failure (CHF), chronic renal insufficiency (CRI), and post-cardiac surgery. Drugs and dosage regimens vary based on the patient's diagnosis.[1]

The rationale behind using CI diuretics is to overcome the phenomenon known as "diuretic resistance." This phenomenon, also known as tolerance, occurs when the kidneys adapt to chronic high-dose diuretic therapy by stimulating sodium retention.[1]

There are a few well-designed clinical trials that compare the use of CI diuretic therapy to traditional bolus administration. The majority of the studies focus on the use of furosemide (Lasix®), however there is also some information on the use of bumetanide (Bumex®).

The most well studied indication for CI diuretics is CHF. In 2001, Dormans and colleagues conducted a randomized, crossover study of CI furosemide versus an equal dose by bolus injection. 20 patients with New York Heart Association (NYHA) class III or IV heart failure were included. The patients were randomized to receive a dose equal to their maintenance oral dose as CI over 8 hours or as a single bolus injection. The CI consisted of a loading dose of 20% of the total dose followed by 10% of the dose per hour. The investigators found a significantly higher urine output and sodium excretion in the CI group. 5 patients receiving bolus therapy reported reversible hearing loss or tinnitus; however no adverse events were reported in patients treated with CI.[2]

Another randomized crossover study evaluated more conventional doses of furosemide in 9 patients with NYHA class III or IV CHF. Patients received 30 to 40 mg every 8 hours as bolus therapy or a CI consisting of a 30 to 40 mg loading dose followed by 2.5 to 3.3 mg per hour (mg/hr). Again, total urine output and total sodium excretion were significantly higher in the CI group.[3]

CI protocols all begin with a loading dose followed by a constant infusion. For example, 1 protocol for CI furosemide in patients with heart failure is to administer a 100 mg IV bolus dose followed by a continuous infusion of 20 to 40 mg/hr. The infusion rate is doubled every 12 to 24 hours with a maximum rate of 160 mg/hr. This protocol has been evaluated in elderly patients hospitalized for NYHA class IV CHF.[4] Another suggested protocol is to initiate therapy with a loading dose of 40 mg and start an infusion at 0.1 mg/kg/hr (eg, 7 mg/hr in a 70 kg patient).[5] The infusion should be doubled every hour until the patient reaches their target urinary output (eg, greater than or equal to 1 mL/kg/hr). This protocol is less aggressive, but requires increased monitoring of hourly urine output.

The use of CI bumetanide has also been evaluated in heart failure. However, the literature is not as extensive with this drug. The use of this agent may be limited by an increased incidence in the development of musculoskeletal symptoms when infusion rates greater than 2 mg/hr are used.[4] Bumetanide as a CI has also been assessed in patients with severe CRI. Rudy and colleagues conducted a randomized crossover clinical trial of intermittent bumetanide versus CI in patients with severe CRI. 8 adult patients were randomized to receive 12 mg of bumetanide as either two 6-mg bolus doses separated by 6 hours or as a continuous infusion over 12 hours. Patients receiving the CI were given a 1-mg loading dose. The results of this study were similar to that of furosemide in heart failure with better urine output and sodium excretion in the patients receiving CI therapy. Patients also tolerated the CI better. Three patients developed diffuse myalgias during bolus therapy, while no patients reported adverse effects during CI therapy.[6]

A third indication for the use of CI diuretics is in both adult and pediatric patients following cardiac surgery. A study of adult post-open-heart-surgery patients did not reveal a significant difference between CI furosemide and bolus therapy. Diuresis in the CI group was less variable from hour to hour and was sustained throughout the infusion. In contrast, those patients receiving bolus therapy eliminated more than 70% of the total urine volume in the first 2 hours post-dose. This indicates that CI diuretics may be useful when sustained diuresis is warranted. Pediatric post-open-heart-surgery patients required less drug to maintain adequate urine output of greater than 1 mL/kg/hr when treated with CI furosemide versus bolus therapy. There was also more variability in urine output in pediatric patients receiving bolus therapy.[7]

Based on the available literature CI loop diuretics appear to be more efficacious in select patient populations. The use of CI diuretics appears to have the largest role in those patients who are at greatest risk for diuretic resistance, such as patients with severe heart failure, severe chronic renal insufficiency, and following cardiac surgery. However, the wide range of doses and duration of infusions that have been studied does not allow for a standard recommendation regarding the optimal regimen for CI diuretics.

By Sherl Drawdy, PharmD

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AVOID THESE ABBREVIATIONS...AND AVOID PROBLEMS

The following inappropriate abbreviations CANNOT be used. Please use an appropriate abbreviation to write a valid order.

Inappropriate Abbreviation	Appropriate Abbreviation
U	Spell "Units" instead
IU	Spell "International Units" or "Units" instead
µ (Greek mu symbol)	Use "mcg" for micrograms
Doses less than 1 unit	Use leading zero (eg, 0.1 mg)
Doses greater than 1 unit	Do not use trailing zero (ie, 1 mg, not 1.0 mg)
QD or OD	Spell "daily" instead
< or >	Spell "less than" or "greater than"
MSO4	Spell "Morphine"
MgSO4	Spell "Magnesium sulfate"
CC	Use "mL" instead

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EDITOR, DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR, PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN, PHARMACY & THERAPEUTICS COMMITTEE
Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

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SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
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NEW DRUGS & SELECTED BIOLOGICALS APPROVED BY THE FDA IN 2004

GENERIC NAME	TRADE NAME	INDICATION
Acamprosate	Campral®	Alcoholism
Apomorphine	Apokyn®	Hypomobility in Parkinson's disease
Azacitidine†	Vidaza®	Myelodysplastic syndrome
Bevacizumab‡	Avastin®	Colorectal cancer
Cetuximab‡	Erbitix®	Colorectal cancer
Cinacalcet	Sensipar®	Secondary hyperparathyroidism
Clofarabine	Clolar®	Acute lymphoblastic leukemia
Darifenacin	Enablex®	Overactive bladder
Duloxetine	Cymbalta®	Depression
Erlotinib	Tarceva®	Non-small cell lung cancer
Eszopiclone	Lunesta®	Insomnia
Gadobenate Dimeglumine	Multihance®	Diagnostic aid (MRI)
Glutamine	NutreStore®	Short bowel syndrome
Human Secretin	Chirostim®	Diagnostic aid (pancreas)
Hyaluronidase (Bovine)†	Amphadase®	Increase absorption and drug dispersion
Hyaluronidase (Ovine)	Vitrase®	Increase absorption and drug dispersion
Iloprost	Ventavis®	Pulmonary arterial hypertension
Insulin Glulisine	Apidra®	Diabetes
Lanthanum Carbonate	Fosrenol®	Phosphate binder for renal disease
Lutropin Alfa	Luveris®	Infertility
Natalizumab‡	Tysabri®	Multiple sclerosis
Omega-3-Acid Ethyl Esters	Omacor®	Hypertriglyceridemia
Palifermin‡	Kepivance®	Severe oral mucositis
Pegaptanib	Macugen®	Macular degeneration
Pemetrexed	Alimta®	Malignant pleural mesothelioma
Pentetate Calcium Trisodium	Pentetate Calcium Trisodium	Internal radiation contamination
Pentetate Zinc Trisodium	Pentetate Zinc Trisodium	Internal radiation contamination
Pregabalin	Lyrica®	Pain (neuropathic and postherpetic neuralgia)
Rifaximin	Xifaxan®	Travelers' diarrhea
Solifenacin	VESIcare®	Overactive bladder
Technetium (99m Tc) fanolesomab‡	NeutroSpec®	Diagnostic agent (appendicitis)
Telithromycin	Ketek®	Antibiotic
Tinidazole	Tindamax®	Trichomoniasis
Tiotropium†	Spiriva®	Chronic obstructive pulmonary disease
Trospium	Sanctura®	Overactive bladder
Trypan Blue	VisionBlue®	Aid in ophthalmic surgery
Ziconotide	Prialt®	Pain

†Listed in the Shands at UF *Formulary*
‡Biological