SHANDS Jacksonville

DRUG UPDATE

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FORMULARY UPDATE

The P&T Committee met on August 20, and September 17, 2007. The following is a summary of the business conducted:

ADDED:

- Pregabalin (Lyrica®)
- Conivaptan (Vaprisol®)

DELETED:

- Repository corticotropin injection in 16% gelatin (Acthar Gel®)

CRITERIA FOR USE:

- Thiazolidinediones (piogliazone (Actos®), rosiglitazone (Avandia®)

Pregabalin (Lyrica®) is structurally related to the inhibitory CNS neurotransmitter γ-aminobutyric acid (GABA) and the *Formulary* antiepileptic agent gabapentin. Pregabalin is indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and as adjunctive therapy for adults with partial onset seizures. Its newest indication is for the treatment of fibromyalgia. There are currently no comparative efficacy trials between pregabalin and gabapentin, and many pregabalin placebo-controlled trials excluded patients refractory to gabapentin. Unlike gabapentin, pregabalin is a schedule V controlled substance due to euphoria (1-2%) reported in clinical trials. The usual dosage of pregabalin is 75 mg twice daily or 150 mg three times a day, up to a maximum

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Prescribing

Estimating renal function, should we use Cockroft-Gault or the MDRD equations?

Chronic kidney disease is quickly becoming a world wide public health problem.[1,2] The incidence and prevalence of end-stage renal disease, dialysis, and transplantation have more than quadrupled over the last two decades.[3] The estimated prevalence of established renal failure is around 1400 per million in the United States and over 600 million in the United Kingdom.[2] Measuring filtration function of the kidney or glomular filtration rate (GFR) remains the most important indicator of overall renal function.[1] GFR has become key to proper assessment of kidney disease and in drug dosing.[4] Chronic kidney disease affects renal elimination and other pharmacokinetic processes involved in drug disposition (e.g., absorption, drug distribution, nonrenal clearance [metabolism]).[5] Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes.

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The gold standard of measuring GFR is the measurement of the urinary clearance of exogenous markers, such as inulin. However because this is a complex, expensive, and cumbersome process, it is often impractical for routine clinical practice. To overcome this obstacle, several prediction equations have been developed based on serum creatinine determinations and other patient specific factors. This has resulted in greater clinical utility of GFR prediction.[4,6] Today, the two most widely recommended and used formulas for assessment of renal clearance are the Cockroft-Gault equation[8], and the more recently developed Modification of Diet in Renal Disease (MDRD) Study equation.[7]

The Cockroft-Gault equation was developed in 1976 in a sample of 249 healthy men with serum creatinine at steady state. The equation provides an adjustment factor for women based on a theoretical 15% lower muscle mass.[8] The Cockroft-Gault equation estimates creatinine clearance (CrCl) based on serum creatinine (SCr), age, sex, and body weight (see

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of 600 mg/day. The maximum dose is reduced for patients with renal dysfunction. The most common adverse effects of pregabalin are similar to gabapentin and include dizziness (10-39%), peripheral edema (9-20%), somnolence (7-20%), weight gain (8%), headaches (7%), blurred vision (6-10%), increased appetite (5%), xerostomia (5%), and flatulence (2%). Abrupt withdrawal of pregabalin may cause insomnia, nausea, headache, and diarrhea. Pregabalin should be discontinued gradually over a one-week period. The cost of pregabalin is more than twice that of the highest recommended dose of gabapentin for the treatment of peripheral neuropathy, thus its use should be limited. **The P&T Committee added pregabalin to the *Formulary*.** The approved Criteria for Use will limit its use to the following indications: 1) For adjunctive therapy for partial seizures in patients refractory to treatment with other antiepileptic medications. 2) For treatment of neuropathic pain syndromes (i.e., diabetic peripheral neuropathy, postherpetic neuralgia) in patients who are unable to tolerate gabapentin doses >1200 mg daily or who have failed therapy with gabapentin and one tricyclic antidepressant agent (e.g., amitriptyline, nortriptyline) 3) Management of fibromyalgia.

Conivaptan (Vaprisol®), a nonpeptide, dual antagonist of arginine vasopressin (AVP) V1A and V2 receptors, is indicated for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients. It is administered intravenously for up to four days. Use of this agent will be primarily for the acute treatment of syndrome of inappropriate antidiuretic hormone release (SIADH); however, there have been evaluations in the literature for the use of this class of agents for heart failure (HF). Conivaptan product labeling and clinical trial data do not currently support the use of vasopressin antagonists to improve HF morbidity and mortality. A 4-day course of conivaptan can cost up to $2,800 and use is associated with infusion-site discomfort and drug interactions. **Because overuse and misuse of this product is of concern, the P&T Committee added conivaptan to the Shands Jacksonville *Formulary* and restricted its use to the Division of Nephrology and Hypertension.**

The Criteria for Use for the thiazolidinediones were revised to include information about pioglitazone (Actos®), which was added to the *Formulary* in June due to emerging concerns about the link between rosiglitazone (Avandia®) and a risk of cardiac ischemia. The revision includes data on the recent boxed warning added to the labeling of both agents discussing the potential risk of heart failure during treatment.

Formulary

Acthar Gel added to Non-Formulary/Do Not Stock List

Acthar Gel®, repository corticotropin (ACTH) injection in 16% gelatin is indicated for diagnostic testing of adrenocortical function and treatment of acute exacerbations of multiple sclerosis, myasthenia gravis. It is also used for the treatment of infantile spasms, although this is an unlabeled indication.

The manufacturer for Acthar Gel, Questcor Pharmaceuticals, has recently implemented a price increase from approximately **$1,500/vial to $23,000/vial.** Questor justifies the exponential increase in price necessary to "make manufacturing and distribution of Acthar economically viable on a standalone basis, so that Questor can continue to ensure the availability of Acthar for those patients who need it most and to fund projects that can contribute to the growth of the company." Questor recently submitted a Supplemental New Drug Application to the FDA pursuing formal approval of this drug for the treatment of infantile spasms. There are no FDA-approved medications for this condition. The use of this product at Shands Jacksonville has been low, approximately, 1-2 vials a year.

There are therapeutic alternatives for Acthar Gel in the Shands Jacksonville *Formulary*. For a diagnosis for adrenocortical dysfunction cosyntropin (Cortrosyn®) is available. Alternatives for multiple sclerosis exacerbations include intravenous corticosteroids such as methylprednisolone (Solu-Medrol®).

For infantile spasms, the mainstay of treatment is adrenocorticotropic hormone (ACTH) and conventional antiepileptic medications. Commonly used first-line treatments included in the Shands Jacksonville *Formulary* include ACTH (Cortrosyn®), prednisone, pyridoxine [vitamin B-6]). Second line treatments included in the *Formulary* include benzodiazepines, valproic acid (Depakote®), lamotrigine (Lamictal®), topiramate (Topomax®), and zonisamide (Zonegran®).

Acthar Gel was deleted from the Shands Jacksonville *Formulary* The P&T Committee does not endose its use on campus, therefore, it was added to the non-formulary/do not stock list.

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*(**Cockroft-Gault vs. MDRD** from page 1)*

table).[8] The accuracy and validity of this equation has been evaluated in many publications. Because weight is included in the numerator as a measure of muscle mass, the equation overestimates GFR in patients who are edematous, overweight or obese, and have decreased renal function.[1,9] However, the Cockcroft-Gault equation is the formula used by pharmaceutical manufacturers in dosage modification studies for renal dysfunction.[10]

In contrast, the MDRD formula estimates GFR adjusted for 1.73 m^2 (average body surface area).[11] The equation was derived in 1999 using data from 1628 patients enrolled in the MDRD study.[11] All of the patients enrolled in the MDRD study were persons with chronic kidney disease (CKD),. Healthy subjects were excluded.[11] The original MDRD study equation was based on 6-variables; age; sex; ethnicity; and serum levels of creatinine, urea, and albumin. Subsequently, a 4-variable abbreviated equation was proposed consisting of age; sex; ethnicity; and serum creatinine levels.[9] The 4-variable equation can be seen in the table. Unlike the Cockcroft-Gault equation, the MDRD provides estimates of GFR standardized for body surface area. Race is also taken into account in the equation. Racial differences are known to have an effect on muscle mass, which may be reflected as a higher average serum creatinine.[1] The MDRD equation has been extensively studied and validated to be more accurate than a GFR calculated from a timed 24-hour urine collection.[11] The limitation of MDRD is that it often underestimates the measured GFR in patients with normal renal function.[6] Thus, its application to the general population may lead to overestimation of the presence of CKD. In patients with a GFR lower than 60 mL per minute per 1.73 m^2, the MDRD equation has been shown to be superior to the Cockcroft-Gault equation.[5]

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guideline advocates using the traditional Cockcroft-Gault equation or the MDRD study equation (full or abbreviated) for routine estimation of GFR.[5] While the National Kidney Disease Education Program (NKDEP) of the National Institute of Diabetes and Diseases of the Kidney (NIDDK), National Kidney Foundation (NKF) and American Society of Nephrology (ASN) recommend estimating GFR from serum creatinine using the MDRD Study equation.[12] These equations appear cumbersome; however, both the Cockcroft-Gault and the MDRD Study equations are available on the National Kidney Foundation's website at www.kidney.org/kls/professionals/gfr_calculator.[12] Additionally, GFR calculators for PDA can also be found at http://www.kidney.org/professionals/kdoqi/cap.cfm or http://www.nkdep.nih.gov/professionals/gfr_calculators/gfr_application.htm.

In clinical practice, a combination of both the Cockroft-Gault and MDRD equations are used. The full MDRD equation is used to stage patients' degree of kidney dysfunction, while Cockroft-Gault is used to make drug dosage adjustments.

Estimating GFR from serum creatinine level assumes that renal function is stable and that the serum creatinine measurement is constant.[13] With changing renal function, the serum creatinine level will no longer reflect the true clearance rate, and creatinine should ideally be measured with a timed urine collection, using the midpoint value.[13] Additional instances where a timed 24-hour urine collection may be necessary include: extremes of age, severe malnutrition, paraplegia/quadriplegia, vegetarian diet, rapidly changing renal function, and pregnancy.[12]

In clinical practice, a combination of both the Cockroft-Gault and MDRD equations are used. The full MDRD equation is often used to stage patients' degree of kidney dysfunction. In contrast, the Cockroft-Gault equation is used to make dosage adjustments, since this how drug manufacturers establish their dosing recommendations. It is important for clinicians to take into account acute versus chronic kidney disease, and the patients' stage of kidney dysfunction when estimating renal function.

Due to the large patient population affected by impaired kidney function it is important that healthcare providers are aware of prediction equations and their limitations and interpretation in various patient populations. Understanding these limitations will help physicians and other healthcare providers' better estimate GFR. This will allow for reduced dosing error, decreased adverse reactions, and better overall patient outcomes.

By Melissa Teichman, Pharm.D.

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Table. Equations for estimating renal function [8,11]

Cockroft-Gault Equation

Estimated Creatinine Clearance (ml/min) = $\frac{[140\text{-age (years)} \times \text{weight (kg)}]}{(72 \times \text{Scr (serum creatinine)})}$

Multiply by 0.85 if female

Use ideal body weight Men = 50 + (2.3 x number of inches over 5 feet)
Women = 45.5 + (2.3 x number of inches over 5 feet)

4-variable MDRD Equation

Estimated GFR (ml/min/1.73m^2) = 186 x serum creatinine (mg/dl) $^{-1.154}$ x age (years) $^{-0.203}$ x (0.742 if female) x (1.210 if African-American)

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SHANDS Jacksonville is a major affiliate and teaching hospital of the University of Florida Health Science Center/Jacksonville.

Prepared by the Therapeutic Policy Management Division, Department of Pharmacy and the Pharmacy and Therapeutics Committee, Shands Jacksonville. Drug Information Services 904-244-4185.

Drug Safety

New ceftriaxone (Rocephin®) and IV calcium warnings

Recently, the Food and Drug Administration (FDA) issued a warning due to reports of deaths associated with concomitant infusions of ceftriaxone (Rocephin®) and calcium solutions in neonates.

Post-marketing reports describe eight neonatal deaths related to this interaction. Calcium-containing fluids and ceftriaxone were administered in the same infusion line for four known cases and from separate lines at different times in one other case. Autopsy revealed evidence of crystalline material in the renal and pulmonary vasculature of two neonates; one had evidence of crystals in the lung. Another had evidence of precipitate in the tubing, with death occurring soon after injection of the crystalline material.

These reports have resulted in a contraindication to the labeling of Rocephin, stating that *ceftriaxone must not be co-administered with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition, in neonates (≤ 28 days) because of the risk of precipitation of ceftriaxone-calcium salts*. Based on the pharmacokinetic profile of ceftriaxone, no calcium-containing fluids should be administered within 48 hours of ceftriaxone nor should ceftriaxone be administered within 48 hours of calcium-containing fluids.

Although there are no similar case reports of this interaction in adults, the labeling of ceftriaxone now includes a warning to all age groups due to the theoretical possibility. At this time, there is no data on a potential interaction between oral calcium-containing products or an interaction between IM ceftriaxone and calcium-containing products (oral or IV).

Practitioners should be prudent when using IV ceftriaxone in patients who have received a calcium-containing product, especially in a neonate. If any interactions or adverse effects are discovered, please complete an Adverse Drug Reaction Report and forward to the Department of Pharmacy. Please contact the Drug Information Service at 244-4185 for any other questions.

By Stephen Rolfe, Pharm.D.

(Cockroft-Gault vs. MDRD from page 3)

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