1. **Allopurinol** (GFR <100), significant increase in t½ of active metabolite [1 week in ESRD patients], concerns of interstitial nephritis, exfoliative dermatitis, or hepatitis

|  |  |
| --- | --- |
| Cr Cl | Dose (milligrams)/Interval |
| 100 | 300 mg/day |
| 80 | 250 mg/day |
| 60 | 200 mg/day |
| 40 | 150 mg/day |
| 20 | 100 mg/day |
| 10 | 100 mg/every 2 days |
| 0 | 100 mg/every 2 days |

(Hande et al, 1984) – consistent with Lexi-Comp/KP eFormulary

Alternative dosing scheme based on GFR and 300 mg/24 hours for normal renal function:

|  |  |
| --- | --- |
| GFR | % of Normal Dose |
| > 50 | 75% |
| 10 to 50 | 50% |
| < 10 | 25% |

(Aronoff et al, 1999) – dose adjustment utilized in Drug Prescribing in Renal Failure by Bennett et al.

* The incidence of allopurinol hypersensitivity may be increased in patients with compromised renal function taking a thiazide and allopurinol concomitantly (Prod Info Zyloprim(R), 2000)(Prod Info Aloprim(TM), 99b; Yale et al, 1996). However, in a retrospective of 120 patients (adults) with gout and hyperuricemia whose initial doses were adjusted for creatinine clearance, 68 (57%) eventually required higher than recommended dose titrations to reduce serum uric acid concentrations to less than 390 micromole/liter (6.6 mg/dL). Two of these 68 (3%) were judged to have drug-induced adverse reactions compared to 3 of 52 (6%) patients whose doses matched renal function (Vazquez-Mellado, 2001).
* Patients with renal insufficiency have developed hepatic dysfunction and progressive renal failure, which may be enhanced by thiazide diuretic administration (Ohsawa & Ohtsubo, 1985; Raper et al, 1984; Phanichphant & Boonpucknavig, 1980; Lindsey & Evans, 1978; Boyer et al, 1977; Young et al, 1974).
* In the majority of cases reporting hepatic failure, symptoms developed while receiving allopurinol 300 milligrams/day for 1 to 4 weeks. The most common findings include fever, hepatomegaly, elevated liver function tests, left upper quadrant pain, splenomegaly, jaundice, asterixis, fatigue, anorexia, drowsiness, eosinophilia, arthralgias, myalgias, dermatitis, and diplopia. Liver biopsy revealed focal necrosis, fatty changes, noncaseating granulomas, fibrin ring granulomas, and toxic hepatic centrilobular necrosis. Allopurinol-induced liver injury appears to be enhanced in patients receiving thiazide diuretics or in patients with renal insufficiency. In severe cases pulmonary edema and hypotension developed and proved fatal. However, in the majority of cases, discontinuation of allopurinol lead to prompt improvement (Tam & Carroll, 1989; Vanderstigel et al, 1986; Ohsawa & Ohtsubo, 1985; Raper et al, 1984; Chawla et al, 1977; Simmons et al, 1972; Espiritu et al, 1976; Al-Kawas et al, 1981a).

1. **Anti-infectives** (various)
2. **Acyclovir** (GFR <50), significant neurotoxicity, development or worsening of renal impairment due to crystal nephropathy



* Approximately 1% of patients receiving IV acyclovir have manifested lethargy, tremors, confusion, hallucination, agitation, seizures, or coma (Prod Info Zovirax(R) injection, 2002)(Arndt, 1988). Other central nervous system effects reported include disorientation, delusions, myoclonus, slurred speech, hyperacusis, delirium, dysarthria, fatigue and mania (Prod Info Zovirax(R) injection, 2003)(Saral et al, 1981; Fukunishi et al, 1994). Often these symptoms are associated with high doses of acyclovir, or concomitant neurotoxic drugs, or impaired renal function (Wade & Meyers, 1983; Cohen et al, 1984; Jones & Beier-Hanratty, 1986; Thomson et al, 1985; Feldman et al, 1988; Johnson et al, 1994). Also, these side effects may be more marked in older adults or in patients with renal impairment (Prod Info Zovirax(R) Capsules, Tablets, Suspension, 2003). Hemodialysis may be useful for patients with end-stage renal dysfunction, who are experiencing toxicity with acyclovir (Krieble et al, 1993).
* Neurotoxicity is more common in patients receiving intravenous acyclovir; however, neurotoxicity may occur with oral administration in the presence of severe renal failure (Swan & Bennett, 1989; MacDiarmaid-Gordon et al, 1992; Beales et al, 1994). Neurotoxicity progressing to coma has been described in a case report (Rajan et al, 2000).
* Renal dysfunction due to acyclovir is the result of crystal nephropathy, which can occur when the maximum solubility of free drug is exceeded. Acute tubular necrosis, without crystalluria, has also been reported with intravenous acyclovir (Becker et al, 1993). Although renal impairment occurs most frequently with bolus or infused intravenous acyclovir, oral acyclovir has been reported to cause renal failure (Prod Info Zovirax(R) Capsules, Tablets, Suspension, 2003; Eck et al, 1991; Johnson et al, 1994). Concurrent use of nephrotoxic drugs, preexisting renal disease, and dehydration predispose to the development of renal impairment (Bradley et al, 1997). In most cases renal dysfunction is transient and resolves spontaneously after acyclovir is discontinued (Peterslund et al, 1988). Renal function should be monitored closely in patients receiving intravenous acyclovir, in those predisposed to dysfunction and adequate hydration should be maintained throughout treatment to assure a high urine flow. It appears safe to reinitiate therapy with the drug at lower doses following subsidence of renal dysfunction (Sawyer et al, 1988).

1. **Imipenem** (GFR <50), Increased seizure risk and thrombocytopenia have been reported in patients with significant renal dysfunction. Meropenem may be preferred.

**DO NOT use concomitantly with ganciclovir**: May enhance the adverse/toxic effect of Imipenem. May increase risk of seizures. *Risk X: Avoid combination*

* Seizures have occurred during imipenem/cilastatin therapy (Lane et al, 1996; Calandra et al, 1985a; Solomkin et al, 1985b; Brotherton & Kelber, 1984a). The incidence of seizures appears to be about 1% to 1.5% (Calandra et al, 1985a). However, the manufacturer indicates an incidence of 0.4% (Prod Info PRIMAXIN(R) IM injection, 2006). Risk factors associated with seizures in patients being treated with imipenem/cilastin include preexisting central nervous system lesions or disorders, renal dysfunction, exceeding the recommended dose, and Pseudomonas aeruginosa infection. The average time to onset of seizures is seven days (Calandra et al, 1988). Imipenem/cilastatin should be used cautiously in patients with impaired renal function; adjusting the dose may not be adequate to prevent seizures (Leo & Ballow, 1991a; Tse et al, 1987); (Fitzsimmons et al, 1987)(Drusano, 1986; Park & Parker, 1986).
* The average time of onset of seizures was seven days after the start of therapy. In the retrospective study of 1754 patients receiving imipenem/cilastatin revealed 7% of patients who received a dose in excess of the manufacturer's recommendations seized while 1.6% of patients who were dosed by the recommendations seized. Of the patients who experienced seizures during treatment, 21% (10/48) had a Clcr of <20 mL/minute, while only 3% of non-seizing patients had low clearance (Calandra et al, 1988).

1. **Valacyclovir** (GFR <50), significant neurotoxicity

* Development or worsening of renal impairment due to crystal nephropathy (see acyclovir for further comments and details)

1. **Biphosphanates** (various)
2. **Alendronate** (GFR < 35), not well-studied

* Dosage adjustment is NOT necessary for patients with a Clcr >35 mL/min. Alendronate is NOT recommended for patients with a Clcr <35 mL/min. Since alendronate is eliminated by the kidneys, greater accumulation especially in bone may be expected in patients with impaired renal function (Prod Info FOSAMAX(R) TABLETS AND ORAL SOLUTION, 2005)
* A significant portion of a dose of **alendronate** is eliminated unchanged in the urine (Fleisch, 1994b; Averbuch, 1993a; Inzerillo, 1994a), and lower doses (or avoidance) of the drug are indicated in patients with renal impairment.

1. **Zoledronic acid** (GFR <35), nephrotoxicity
2. Reclast®

* Reclast should not be used in patients with severe renal impairment (Clcr <35 mL/min) due to lack of adequate clinical experience in this population.
* No dosage adjustment is required in patients with a Clcr of ≥ 35 mL/min.
* Risk of renal impairment may increase with underlying renal disease and dehydration secondary to fever, gastrointestinal losses, diuretic therapy, etc.
* Renal impairment has been observed following the administration of zoledronic acid, especially in patients with preexisting renal compromise or other risk factors including concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Reclast administration. Renal impairment has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis occurred in patients with underlying moderate to severe renal impairment. Renal impairment may lead to increased exposure of concomitant medications that are primarily renally excreted.
* Serum creatinine should be measured before each Reclast dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; consider interim monitoring of serum creatinine in at-risk patients. Patients, especially those receiving diuretic therapy, should be appropriately hydrated prior to administration of Reclast. Reclast should be used with caution with other nephrotoxic drugs. Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidney (Prod Info RECLAST(R) IV injection, 2011).

1. Zometa®

* 4 mg as a single-dose intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with Clcr of >60 mL/min
* Reduce the dose for patients with renal impairment [*see table below*]
* Renal toxicity may be greater in patients with renal impairment. Do not use doses greater than 4 mg. **Treatment in patients with severe renal impairment is not recommended**.
* In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.
* Reduced Doses for Patients with Baseline CrCl <60 mL/min:

|  |  |
| --- | --- |
| Baseline Creatinine Clearance (mL/min) | Zometa Recommended Dose \* |
| 50-60 | 3.5 mg |
| 40-49 | 3.3 mg |
| 30-39 | 3.0 mg |

\*Doses calculated assuming target AUC of 0.66 (mg•hr/L) (CrCl=75mL/min)

* During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration.
* In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be reinitiated at the same dose as that prior to treatment interruption (Prod Info ZOMETA(R) IV injection, 2011).

1. **Risedronate** (GFR <30), not well-studied

* No dosage adjustment for risedronate is necessary for patients with Clcr ≥30 mL/min. Risedronate is NOT recommended in patients with a Clcr <30 mL/min (Prod Info ACTONEL(R) oral tablets, 2008; Prod Info ACTONEL(R) with Calcium oral tablets, 2006).
* A retrospective analysis of data pooled from 9 randomized, double-blind, placebo-controlled, phase 3 trials (n=9883) showed that oral risedronate 5 milligrams per day for up to 3 years was safe and effective in preserving bone mineral density (BMD) and reducing new vertebral fractures in osteoporotic women with mild, moderate, or severe renal impairment. Patients included in the analysis were those who had age-related renal impairment (Clcr <80 mL/min). The Clcr was estimated using the Cockroft and Gault method, and patients were classified as having mild (Clcr 50 to 80 mL/min; n=4353), moderate (Clcr 30 to 49 mL/min; n=4071), and severe (Clcr less than 30 mL/min; n=572) renal impairment (Miller et al, 2005).
* One study has proposed deferring dose adjustments for patients with Clcr above 20 mL/min (Mitchell et al, 2000). Renal clearance of risedronate was decreased by about 70% in patients with severe renal impairment.

1. **Digoxin** (GFR <50), dosage of **digoxin** must be reduced in renal insufficiency (Marcus, 1966).

* The most reliable indicator of **digoxin** excretion is creatinine clearance (Doherty & Kane, 1973)
* The volume of distribution of **digoxin** can decrease by as much as 50% in patients with renal failure (Doherty et al, 1970a; Anderson et al, 1976a). However, it is not clear whether or not dosage should be reduced corresponding to the reduced volume of distribution, as tissue uptake (including myocardial uptake) of **digoxin** is reduced in renal failure (Jusko, 1978). The pharmacologic and clinical effects of this reduced uptake are not clear, but increased digitalis tolerance has been reported in uremic patients (Kramer et al, 1978). Some investigators prefer digitoxin over **digoxin** in renal failure patients, since digitoxin pharmacokinetics are not as affected by impaired renal function (Rasmussen et al, 1972; Jelliffe et al, 1970; Anderson et al, 1976a; Keller et al, 1980).
* Patients with normal renal function will excrete 35% to 40% of **digoxin** body stores daily, in contrast to 14% daily elimination of total body stores in anephric patients (Jelliffe, 1968; Anderson et al, 1976a).

1. **Enoxaparin** (GFR <50), bleeding complications – DO NOT USE in patients with GFR <30 (Nephrology concensus)

* Enoxaparin has not been FDA approved for use in dialysis patients. It's elimination is primarily via the renal route. Serious bleeding complications have been reported with use in patients who are dialysis dependent or have severe renal failure. LMWH administration at fixed doses without monitoring has greater unpredictable anticoagulant effects in patients with chronic kidney disease. If used, dosages should be reduced and anti-Xa activity frequently monitored, as accumulation may occur with repeated doses. Many clinicians would not use enoxaparin in this population especially without timely anti-Xa activity assay results.
* In subjects with mild to moderate renal impairment (Clcr 30 to 80 milliliter/minute), anti-factor Xa exposure represented by AUC is marginally increased after repeated doses of enoxaparin 40 mg subcutaneously once daily compared to healthy volunteers. In patients with severe renal impairment (CrCl <30 mL/min), the AUC at steady state is increased by 65% after repeated doses compared to healthy volunteers (Prod Info Lovenox(R), 2003).
* Based on a prospective, non-randomized, open-label study (n=233), anti-Xa concentrations measured 4 hours post-injection were higher and more likely to reach supratherapeutic levels among patients with moderate-to-severe renal impairment compared with individuals with normal renal function; therefore, dosing adjustment of enoxaparin may be necessary for severe renally-impaired individuals to maintain target anti-Xa therapeutic range. Patients were treated with either 1 milligrams per kilogram (mg/kg) every 12 hours or 1.5 mg/kg every 24 hours. With twice-daily dosing, the mean anti-Xa levels were 1.06 (95% confidence interval (CI), 0.99 to 1.14) in patients with calculated Clcr >50 mL/min, 1.25 (95% CI, 1.12 to 1.39) in patients with moderate renal impairment (Clcr 30 to 50 mL/min), and 1.27 (95% CI, 1.15 to 1.4) in individuals with severe renal impairment (Clcr l 10 to 30 mL/min). Once-daily administration of enoxaparin resulted in similar and overlapping anti-Xa levels: 1.1 (95% CI, 1 to 1.2), 1.21 (95% CI, 1.09 to 1.33), and 1.18 (95% CI, 0.92 to 1.44), respectively. The analysis suggested that anti-Xa levels increased by 0.03 international units/mL for every 10-mL/min decrease in CrCl (Bazinet et al, 2005).
* A study with 532 patients (34% normal renal function, 36% mild renal impairment, 20% moderate renal impairment, and 10% severe renal impairment) found that dosage adjustments for enoxaparin in patients treated for non-ST-segment elevation in acute coronary syndrome with Clcr <50 mL/min should be considered. All patients, regardless of renal function, should receive 1 mg/kg subcutaneously for the first dose, then dose reductions should be done based on Clcr. In patients with moderate renal impairment (Clcr from 30 to 49 mL/min), the subsequent doses should be 0.8 mg/kg subcutaneously every 12 hours. In patients with severe renal impairment (Clcr <30 mL/min), the subsequent doses should be 0.66 mg/kg every 12 hours. These dosage adjustments should be considered in order to keep peak anti-Xa activities within the target range of 0.5 to 1.2 international units/milliliter (Hulot et al, 2005).

1. **Exenatide** (GFR < 30), acute renal failure, renal insufficiency

* **BYETTA should not be used in patients with severe renal impairment (Clcr < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation**
* In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects.
* Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (Clcr 30 to 50 mL/min).
  + There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies (Prod Info BYETTA(R) injection, 2010).
* **From April 2005 through October 2008, FDA received 78 cases of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency), in patients using Byetta. Some cases occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing kidney problems.**
* **Byetta should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease.**
* **Caution should be applied when initiating or increasing doses of Byetta from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min).**
* **Monitor patients carefully for the development of kidney dysfunction, and evaluate the continued need for Byetta if kidney dysfunction is suspected while using the product (FDA Safety Update for Healthcare Professionals, 11/9/2009).**

1. **Fondaparinux** (GFR <50), bleeding complications

* **DO NOT USE in patients with GFR <30**
* Specific dosing recommendations in patients with renal impairment are not available. The clearance of fondaparinux is approximately 25% lower in patients with mild renal impairment (Clcr between 50 to 80 mL/min), approximately 40% lower in patients with moderate renal impairment (Clcr 30 to 50 mL/min), and approximately 55% lower in patients with severe renal impairment (Clcr <30 mL/min) when compared to patients with normal renal function. Use of fondaparinux in patients with Clcr <30 mL/min is contraindicated (Prod Info ARIXTRA (R) subcutaneous injection, 2008).
* Increasing renal impairment increases the risk of hemorrhage in patients administered fondaparinux. The occurrence of major bleeding in patients receiving prophylactic fondaparinux in hip fracture, hip replacement, or knee replacement surgery was 1.6%, 2.4%, 3.8% and 4.8% in patients with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment, respectively. The occurrence of major bleeding in patients receiving therapeutic fondaparinux for deep vein thrombosis and pulmonary embolism was 0.4%, 1.6%, 2.2% and 7.3%, in patients with normal function, mild, moderate and severe renal impairment, respectively. The use of fondaparinux is therefore contraindicated in patients with a Clcr <30mL/min. Caution should also be exercised when used in patients with mild to moderate renal impairment (Prod Info ARIXTRA (R) subcutaneous injection, 2008).

1. Gadolinium-Based Contrast Agent (GFR <30), Nephrogenic Systemic Fibrosis

* **Black Box Warning**: Exposure to GBCAs increases the risk for NSF in patients with:
  + acute or chronic severe renal insufficiency (GFR <30 mL/min/1.73m2), or
  + acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
* NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
* Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
* Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
* When administering a GBCA, do not exceed the dose recommended in product labeling.  Allow sufficient time for elimination of the GBCA prior to any readministration.
* Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.
* For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination.  However, it is unknown if hemodialysis prevents NSF.
* Determine the renal function of patients by obtaining a medical history or conducting laboratory tests that measure renal function prior to using a GBCA.
* The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown (no report to date).
* Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs.  These reports have not always identified a specific agent.  Where a specific agent was identified, the most commonly reported agent was Omniscan, followed by Magnevist and OptiMARK.  NSF has also developed following the sequential administration of Omniscan and MultiHance and Omniscan and ProHance.  The distribution of the number of reports for the individual GBCAs may relate to multiple factors, including more limited use of some GBCAs, under-reporting of NSF, characteristics of the agent and a lack of patients’ complete GBCA exposure history studies (Prod Info OMNISCAN(R) intravenous injection, 2007) (FDA Alert 5/23/2007)

1. **Glyburide** (GFR <50, per literature, <60 mL/min per KPHI criteria), increased risk of hypoglycemia due to increased duration of active metabolites

* Because glucose homeostasis is impaired and insulin clearance decreased in renal insufficiency, **glyburide** is relatively contraindicated in the presence of severe renal insufficiency due to the risk of profound and prolonged hypoglycemia (Asmal & Marble, 1984a; Jackson & Bressler, 1981b; Paice et al, 1985a). Conservative initial and maintenance doses should be used in patients with renal failure to avoid hypoglycemia (Prod Info Micronase(R), 1997; Prod Info Glynase(R), 1997).
* **Glyburide** is NOT recommended in patients with a Clcr <50 mL/min because as much as 50% of a dose may be eliminated unchanged in the urine (Bennett et al, 1994).
* **Per KPHI P&T, glyburide use limited to 1) members < 65 years old AND 2) GFR > 60mL/min**

1. **Hydrochlorothiazide** (GFR<30), ineffective

* Avoid use when Clcr <10 mL/minute. Usually ineffective with GFR <30 mL/min. May be effective at lower GFR in combination with a loop diuretic.
* Investigators (Bennett et al, 1987) indicate that no specific dosage adjustment is necessary in patients with mild to moderate renal failure.
* Patients with renal failure are usually refractory to hydrochlorothiazide. Hydrochlorothiazide should not be used in patients with a serum creatinine >2.5 mg/dL (Anon, 1993c). Some clinicians do not recommend hydrochlorothiazide if the GFR is <15 to 25 mL/min; other clinicians use furosemide if the GFR is <50 mL/min. Hydrochlorothiazide should be stopped if progressive renal failure is evident by increasing non-protein nitrogen, increasing blood urea nitrogen, and increasing serum creatinine (Anderson & Kepler, 1975a). Hydrochlorothiazide itself decreases GFR; this may aggravate renal failure (Gilman et al, 1990e).

1. **Meperidine** (GFR <50), decreased seizure threshold, with accumulation of neurotoxic metabolite

* No dosage adjustment is necessary in patients with mild renal failure (GFR >50 mL/min) (Bennett et al, 1994). However, patients with moderate renal failure (GFR 10 to 50 mL/min) should receive 75% of the normal dose at the usual intervals and patients with severe renal failure (GFR <10 mL/min) should receive 50% of the normal dose at the usual intervals.
* Normeperidine, a metabolite of meperidine, is a CNS excitotoxin which can accumulate with repetitive dosing and can cause anxiety, tremors, myoclonus, and generalized seizures (Kaiko et al, 1983a). Patients using meperidine for more than 2 days, or patients with pre-existing renal impairment, sickle-cell disease, or central nervous system (CNS) disease, or patients receiving meperidine doses of greater than 600 milligrams/24 hours are particularly at high risk for normeperidine toxicity. Naloxone does not reverse, and may even exacerbate, this hyperexcitability (Szeto et al, 1977a; American Pain Society, 2003). Therefore, meperidine use should be avoided in patients with renal impairment. However, if used, meperidine should not be administered for more than 1 to 2 days. Chronic use is not recommended (American Pain Society, 2003).
* **Per KPHI P&T, meperidine use limited to following indication: shivering, rigors, conscious sedation**

1. **Metformin** (GFR <60), risk of lactic acidosis

* Metformin is substantially excreted by the kidney. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function. Patients with renal function below the limit of normal for their age should not receive metformin.
* In elderly patients, renal function should be monitored regularly; should not be used in any patient ≥80 years of age unless measurement of creatinine clearance verifies normal renal function.
* Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be suspended in patients with dehydration and/or prerenal azotemia. Therapy should be suspended for any surgical procedures (resume only after normal intake resumed and normal renal function is verified).
* Do not administer metformin at the time of and for 48 hours after radiologic studies involving intravascular iodinated contrast materials due to the risk of lactic acidosis. Metformin can be reinstituted only after confirming renal function is normal (Prod Info GLUCOPHAGE(R), GLUCOPHAGE(R) XR oral tablets, extended-release oral tablets, 2006).
* The plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. Per the manufacturer, metformin is contraindicated in the presence of renal dysfunction defined as a serum creatinine >1.5 mg/dL in males, or >1.4 mg/dL in females and in patients with abnormal clearance. Clinically, it has been recommended that metformin be avoided in patients with Clcr <60-70 mL/min (DeFronzo, 1999).

1. **Metoclopramide** (GFR <50), increase in EPS adverse effects

* Based on a normal dose of 10 to 15 milligrams four times daily with normal renal function (Aronoff et al, 1999). The pharmacokinetics of metoclopramide were evaluated after intravenous and oral dosing (10 milligrams) in 6 patients with chronic renal failure. The clearance was shown to be approximately 30% of that found in normal subjects. This difference is not accounted for by the change in renal clearance and suggests impaired metabolism or an alteration in enterohepatic circulation of metoclopramide in renal failure. The mean terminal half-life of both after parenteral and oral therapy was approximately 14 hours, suggesting that the dose of metoclopramide in severe renal failure should be reduced by at least 50% of that normally recommended (Bateman et al, 1981).
* The following dosage reductions are recommended in patients with renal failure:

|  |  |
| --- | --- |
| GFR mL/minute | DOSE RECOMMENDATION |
| 10 or less | 50% of usual dose |
| 10-50 | 75% of usual dose |
| 51 or more | 100% of usual dose |

1. **Morphine sulfate** (GFR <50), neurotoxicity and respiratory depression with decreased clearance of putatively active metabolites

* Morphine primarily undergoes hepatic metabolism to inactive metabolites, which are renally excreted. It would be expected that dosage adjustment in renal failure would not be necessary (Gilman et al, 1990). However, it has been recommended that patients with moderate renal failure (GFR 10 to 50 mL/min) receive 75% of the normal dose at the usual intervals, and patients with severe renal failure (GFR <10 mL/min) receive 50% of the normal dose at the usual intervals; no dosage adjustment is necessary for patients with mild renal failure (GFR >50 mL/min) (Aronoff et al, 1999). These recommendations are based on actual reports of decreased morphine clearance in renal failure patients, and the possibility that morphine-6- glucuronide may have some narcotic activity (Portenoy et al, 1991; Ball et al, 1985). Epidural administration should be done cautiously, since high morphine levels, due to decreased clearance, may take several days to develop (Prod Info Duramorph(R), 1994a).
* Morphine plasma concentrations following intravenous infusion in intensive care patients, as well as morphine clearance, depends on renal function with dose-related plasma levels increasing as renal function deteriorated. Plasma morphine levels were linearly related to plasma creatinine and creatinine clearance; morphine clearance was linearly related to creatinine clearance. The authors emphasize that a reduction in morphine clearance in intensive care patients with impaired renal function can lead to increased elimination half-lives of the drug and neurological impairment (Ball et al, 1985).
* It has been suggested that accumulation of morphine-6-glucuronide might cause toxicity with renal insufficiency. All of the metabolites (ie, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine) have been suggested as possible causes of neurotoxicity (eg, myoclonus).

1. **Nitrofurantoin** (GFR <60), ineffective and risk of pulmonary toxicity; peripheral sensory neuropathy

* Use with caution in patients with G6PD deficiency or in patients with anemia. Therapeutic concentrations of nitrofurantoin are not attained in urine of patients with Clcr<60 mL/minute. Use with caution if prolonged therapy is anticipated due to possible pulmonary toxicity. Acute, subacute, or chronic (usually after 6 months of therapy) pulmonary reactions have been observed in patients treated with nitrofurantoin; if these occur, discontinue therapy immediately; monitor closely for malaise, dyspnea, cough, fever, radiologic evidence of diffuse interstitial pneumonitis or fibrosis.
* Normal **nitrofurantoin** doses in patients with mild renal failure (GFR more than 50 mL/min) is recommended, but in patients with moderate to severe renal failure (GFR less than 50 mL/min), the use of **nitrofurantoin** should be avoided (Bennett et al, 1987).
* Patients with moderate to severe renal failure should not receive **nitrofurantoin** since it is ineffective with GFR below 20 to 30 mL/min and peripheral sensory neuropathy may occur with a GFR of 10 to 50 mL/min due to metabolites (Felts et al, 1971; Goff et al, 1968; Sachs et al, 1968; Sullivan et al, 1975; Bennett et al, 1987).

1. **NSAIDs**, nephrotoxicity, due to dose-dependent decrease in prostaglandin synthesis

* Analgesics, including NSAIDs and COX-2 inhibitors, have the potential for causing **nephrotoxicity**, especially in high risk patients (eg, congestive heart failure, hepatic cirrhosis, the nephrotic syndrome, hypertension, sepsis, diabetes mellitus, hypovolemia, chronic renal insufficiency). Although case reports of sulindac-induced **nephrotoxicity** are available, it may be a better choice for use in high risk patients due to a favorable metabolic pathway. Regardless of the agent selected, early and frequent monitoring of the patient's serum creatinine is suggested to detect changes in renal function as soon as possible. Randomized controlled trials have demonstrated that the selective COX-2 inhibitors celecoxib and rofecoxib can impair renal function in healthy patients. Therefore, it appears that celecoxib and rofecoxib have similar effects on renal function as traditional NSAIDs. Drug discontinuation is the recommended treatment. Upon discontinuation of analgesic therapy, analgesic- induced renal insufficiency usually reverses, regardless of whether a nonspecific COX inhibitor or COX-2 specific inhibitor is used.
* NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.
* Ibuprofen may precipitate acute renal failure in patients, who are dependent on renal prostaglandins for maintenance of renal blood flow (FDA, 2005; Prod Info Motrin(R), 1999g; Fong & Cohen, 1982; Kimberly et al, 1979); (Kovesi et al, 1998)(Adams et al, 1967); (Van Biljon, 1989). A case of acute renal failure occurring in a preterm infant who received ibuprofen for closure of Patent ductus arteriosus has also been identified (Erdeve et al, 2008).
* Ibuprofen use has been associated with interstitial nephritis, and papillary necrosis (Prod Info Motrin(R), 1999g); (DuBose & Molony, 1994)(Schlondorff, 1993; Spierto et al, 1992; Whelton & Hamilton, 1991; Piepho et al, 1991; Kleinknecht et al, 1986; Shah et al, 1981). Reactions of this type may also occur in children (Primack et al, 1997).
* Ibuprofen use has also been associated with nephrotic syndrome, and membranous nephropathy (Prod Info Motrin(R), 1999g); (DuBose & Molony, 1994)(Schlondorff, 1993; Spierto et al, 1992; Whelton & Hamilton, 1991; Piepho et al, 1991; Kleinknecht et al, 1986; Shah et al, 1981). Reactions of this type may also occur in children (Primack et al, 1997). (Radford et al, 1996); (Morgenstern, 1989; Justiniani, 1986).
* Ibuprofen use has also been associated papillary necrosis (FDA, 2005; Prod Info Motrin(R), 1999g); (DuBose & Molony, 1994)(Schlondorff, 1993; Spierto et al, 1992; Whelton & Hamilton, 1991; Piepho et al, 1991; Kleinknecht et al, 1986; Shah et al, 1981). Reactions of this type may also occur in children (Primack et al, 1997).
* All NSAIDs inhibit cyclooxygenase, the enzyme required for conversion of arachidonic acid to prostaglandins. Renal prostaglandins are produced as needed in response to vasoactive hormones (eg, angiotensin II, vasopressin, norepinephrine, endothelin), cytokines, hypoxia, ischemia, or cellular disturbances. All of these stimuli cause release of arachidonic acid with subsequent synthesis of PGI2, PGE2, and PGF2a, the predominant renal prostaglandins. Renal prostaglandins attenuate the effects of vasoconstrictors (eg, angiotensin II, norepinephrine, vasopressin, endothelin) by causing vasodilation. This ultimately maintains renal blood flow and glomerular filtration. The other major effects of renal prostaglandins include increased renin release and increased diuresis and natriuresis.
* Alterations in the pharmacokinetics of NSAIDs may contribute to nephrotoxicity. Elderly patients have a decrease in total body water and a lower serum albumin, which increases the free NSAID serum concentration and possibly the drug effect. Impaired liver function potentially decreases metabolism of an NSAID to inactive metabolites, which increases the half-life of the active drug. Since up to 50% of unchanged drug and the metabolites are eliminated by the kidney, decreased renal function increases the duration of effect of the active drug.

1. **Phenazopyridine** (GFR <50), toxicity [hematologic, renal] due to decreased clearance

* It has been recommended that the dosage interval for **phenazopyridine** dosage interval be increased in patients with mild renal failure (GFR >50 mL/min) to every 8 to 16 hours. The drug should not be used in patients with moderate to severe renal failure (GFR <50 mL/min) (Bennett et al, 1980).
* A yellow discoloration of the skin or sclera may indicate an accumulation of **phenazopyridine** due to impaired renal excretion and may require discontinuation of the agent (Prod Info Pyridium(R), 1997a).
* Hemolytic anemia has been observed during therapy with normal doses and following overdoses of phenazopyridine (Greenberg, 1976; Loughner & Bennett, 1980; Jeffery et al, 1982; Green et al, 1979). Hemolysis has been associated with some cases of methemoglobinemia due to phenazopyridine toxicity (Greenberg & Wong, 1964; Greenberg, 1976; Jeffery et al, 1982; Cohen & Bovasso, 1971).
* Methemoglobinemia has been reported during phenazopyridine therapy. Most cases are secondary to overdose or in patients with renal failure. However, methemoglobinemia has been observed in patients with normal renal function taking therapeutic doses (Terrell et al, 1988; Cohen & Bovasso, 1971; Randazzo et al, 1975; Green et al, 1979; Jeffery et al, 1982; Zimmerman et al, 1980). Methemoglobinemia usually occurs within 2 to 3 hours after ingestion of phenazopyridine, but may be delayed. (Wieland et al, 1983).
* Several cases of acute renal failure with transient elevations of creatinine and BUN have been reported with phenazopyridine. Drug withdrawal is associated with clinical improvement (Alano & Webster, 1970; Eybel et al, 1974; Green et al, 1979; Engle & Schoolwerth, 1981). Patients should receive phenazopyridine cautiously and in reduced dosage in the presence of renal impairment. Transient acute renal failure may result from large doses or prolonged use (Tomlinson et al, 1983; Sharon et al, 1986).

1. **Phenytoin** Sedation, confusional states, or cerebellar dysfunction

* Loss of motor coordination may occur at higher total serum concentrations, or at lower total serum concentrations when the free fraction of phenytoin is increased (↓ protein binding + ↑ volume of distribution). Closely monitor free phenytoin levels.
* No specific dose adjustment is recommended (Bennett et al, 1994). However, serum phenytoin protein binding is altered in uremia which can effect proper interpretation/evaluation of serum phenytoin concentrations (Blum et al, 1972; Letteri et al, 1971; Reidenberg et al, 1971). The fraction of unbound phenytoin increases as renal function decreased, partially due to decreases in serum albumin (Liponi et al, 1984). In patients with renal disease, the following equation has been used to relate the measured, or observed, phenytoin concentration to the phenytoin concentration one would expect to measure if there was normal protein binding (Evans et al, 1992):

C (observed)

C (normal) = -------------------------

(0.1 x albumin) + 0.1

C (normal) = normal serum phenytoin concentration in nonuremic patients  
C (observed) = observed serum phenytoin concentration in uremic patients

1. **Probenecid** (GFR <50), ineffective

* In chronic renal impairment probenecid may not be effective when the GFR is <30 mL/min. However, in moderate renal insufficiency to maintain normal serum uric acid levels or uric acid excretion rates above 700 milligrams/24 hours, the dosage may require increasing in increments of 500 milligrams every 4 weeks to a maximum recommended dose of 2 grams/day in 4 divided doses (Prod Info Benemid(R), 1998c).
* Practitioners recommend that probenecid be avoided in patients with moderate to severe renal failure (GFR <50 mL/min) due to inefficacy in this condition (Bennett et al, 1987a). No dosage adjustment is necessary for patients with mild renal failure (GFR >50 mL/min).
* Probenecid is not effective and therefore not recommended for the reduction of uric acid levels in patients with moderate to severe renal failure (Clcr <50 mL/min) (Hawkins, 1989).

1. **Spironolactone** (dose adjust in GFR <50, avoid in GFR <10), hyperkalemia

* Increasing the dosing interval to every 6 to 12 hours in patients with mild renal failure (GFR >50 mL/min) and every 12 to 24 hours in patients with moderate renal failure (GFR 10 to 50 mL/min) has been recommended (Bennett et al, 1987). It is recommended that patients with severe renal failure (GFR <10 mL/min) avoid the use of drug.
* Severe hyperkalemia (serum potassium levels greater than 7) may result in paralysis, flaccid paraplegia and cardiac arrhythmias with subsequent cardiovascular collapse (Rado et al, 1968a; Rado et al, 1968b; Herman & Rado, 1966; Pongpaew et al, 1973). In most cases serious hyperkalemia with potentially fatal consequences occur in patients receiving spironolactone with impaired renal function.
* Spironolactone is frequently reported to cause hyperkalemia particularly when used in patients with impaired renal function, those receiving potassium chloride therapy, elderly patients, or patients with diabetes (McGeown, 1987). An incidence as high as 40% of all patients experiencing adverse reactions to spironolactone has been reported for hyperkalemia (Greenblatt & Koch-Weser, 1973b). Severe hyperkalemia (serum potassium levels greater than 7) may result in paralysis, flaccid paraplegia and cardiac arrhythmias with subsequent cardiovascular collapse (Rado et al, 1968a & b)(Herman & Rado, 1966; Pongpaew et al, 1973). In most cases serious hyperkalemia with potentially fatal consequences occur in patients receiving spironolactone with impaired renal function.

1. **Sodium phosphate** (underlying kidney disease, especially GFR <30), acute phosphate nephropathy

* **Black Box Warning**: There have been rare, but serious reports of acute phosphate nephropathy in patients who received oral sodium phosphate products for colon cleansing prior to colonoscopy. Some cases have resulted in permanent impairment of renal function and some patients required long-term dialysis. While some cases have occurred in patients without identifiable risk factors, patients at increased risk of acute phosphate nephropathy may include those with increased age, hypovolemia, increased bowel transit time (such as bowel obstruction), active colitis, or baseline kidney disease, and those using medicines that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteriodal anti-inflammatory drugs [NSAIDs]).
* Administration of sodium phosphate products prior to colonoscopy for colon cleansing has resulted in fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias. These fatalities have been observed in patients with renal insufficiency, in patients with bowel perforation, and in patients who misused or overdosed sodium phosphate products. It is recommended that patients receiving OsmoPrep be advised to adequately hydrate before, during, and after the use of OsmoPrep.
* There have been rare, but serious, reports of renal failure, acute phosphate nephropathy, and nephrocalcinosis in patients who received oral sodium phosphate products (including oral sodium phosphate solutions and tablets) for colon cleansing prior to colonoscopy. These cases often resulted in permanent impairment of renal function and several patients required long-term dialysis. The time to onset is typically within days; however, in some cases, the diagnosis of these events has been delayed up to several months after the ingestion of these products (Product Info OsmoPrep(R) tablets, 2009)