C. Pharmacologic Pain Management in Patients with CKD

Pharmacologic considerations in CKD include concerns about medications causing kidney impairment (e.g., NSAIDS) and the need to account for renal elimination of medications or their metabolic products, which may be associated with increased risk of side effects (e.g., morphine, hydrocodone). We will briefly highlight common challenges in managing medications for pain in CKD.

NSAIDs in CKD

NSAIDs may cause gastrointestinal, cardiovascular, and kidney adverse events. By blunting prostaglandin-associated regulation of renal hemodynamics, NSAIDs can induce renal ischemia.(298) NSAIDs can also increase blood pressure, cause edema and sodium retention (mostly mild), induce hyperkalemia, and contribute to heart failure.(300) Fortunately, NSAID-induced kidney injury is typically reversible with prompt discontinuation.(298)

What is the risk of NSAID induced kidney injury (AKI or CKD)?

Observational studies demonstrate that nephrotoxic risks of NSAIDs are modest, somewhat predictable, and may be less than risks associated with alternative medications. Patients at higher risk for AKI include those with heart failure, cirrhosis, CKD, or dehydration,(300) as well as those on medications that may alter kidney blood flow, such as RAASi, diuretics,(301) and calcineurin inhibitors.(302) In non-CKD populations, observational studies have revealed conflicting results regarding NSAID-induced kidney injury, with some finding no association with incident CKD (303) and others demonstrating an increase in relative risk with risk generally increasing based on intensity or duration of NSAID exposure.(304-307) While the trend towards increased risk of incident CKD in more recent larger population studies is consistent, the absolute risks are small when reported. Nelson et al. demonstrated an excess of 17 CKD events per 100,000 exposed Active-Duty U.S. service members.(306) There is even less information regarding the risk of developing NSAID-associated renal injury in patients with CKD, in part because those with kidney dysfunction are often excluded from prospective clinical trials. One meta-analysis supported an increased risk of NSAID-associated AKI with HR of 1.7 in patients with pre-existing CKD (308) and an absolute risk of 4% in NSAID exposed versus non-exposed individuals. However, the data reported within the individual trials in that meta-analysis varied by an order of magnitude (e.g., OR: 1.05 to 5.25), suggesting the presence of different populations with differing NSAID risks to a degree that pooled/average numbers should be interpreted with skepticism.

What is the risk of topical NSAID versus systemic NSAID?

Topical NSAIDs are recommended for use in knee osteoarthritis based on evidence of equivalent efficacy for improving pain and function and superior systemic adverse effect profiles compared to oral NSAIDs (see VA/DOD CPG for the Non-Surgical Management of Hip & Knee Osteoarthritis). Multiple meta-analyses of RCTs have shown that adverse effects of topical NSAIDs are similar to placebo, except for increased local adverse effects, mostly mild skin reactions.(309-311) Diclofenac is a topical NSAID approved in the U.S. for osteoarthritis. In a pooled safety analysis of 7 RCTs of topical diclofenac 1.5% use, among 138 patients using topical diclofenac for 4-12 weeks, no patients experienced a serious kidney adverse event; changes in BP and kidney function were similar between the diclofenac and placebo/control groups.(312) Studies with topical diclofenac have shown that the level attained in blood is 0.4-2.2% of the maximum serum