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EDITORIAL

DRUG METABOLISM AND ACTIVE DRUG METABOLITES IN RENAL FAILURE

A relatively small number of drugs are eliminated from the body by renal excretion of the drug itself. Some of these drugs are:

colistin
penicillin
procainamide
digoxin
aminoglucoside antibiotics
cycloserine
ethambutol
methotrexate
tetracycline

Methods for reducing the usual doses of these drugs for patients requiring chronic dialysis have been published in various places and are now standard practice (1-4).

Most drugs, however, are not excreted unchanged. They are biotransformed in the body to various metabolites which are eventually excreted. The major pathways of drug biotransformation, oxidation and glucuronide conjugation, appear to be normal in renal failure. Several minor pathways, including ester hydrolysis and reduction, seem slow (5). However, irrespective of whether the biotransformation pathway is normal or slow, the end metabolic products of the drug will accumulate in the patient with renal failure.

Traditionally, these biotransformation pathways have been considered detoxication pathways. The final metabolites of drugs have been considered pharmacologically inert, and their build-up in patients with end stage renal disease has been ignored. Yet, recent studies have demonstrated pharmacologic activity of many drug metabolites, and their accumulation in renal failure can lead to unanticipated effects.

Muscle weakness and tenderness together with a rise in serum creatine kinase were noted in 5 uremic patients being treated with 1-2g of clofibrate daily. Marked accumulation of both free and total chlorophenoxyisobutyric acid, the active metabolite of clofibrate, was found in the serum of 3 patients in whom it was sought. When clofibrate was stopped, the muscle symptoms and creatine kinase elevation subsided (6).

Oxypurinol is an active metabolite of allopurinol that is normally excreted in the urine. Plasma levels of oxypurinol in patients with poor renal function taking allopurinol are several fold higher than the oxypurinol levels in subjects with normal kidneys. This has been correlated with a higher incidence of side effects in renal failure patients given allopurinol than in patients with healthy kidneys (7).

Sulfonamides are both excreted unchanged and biotransformed by acetylation with subsequent urinary excretion of the acetylated metabolite. While reduction of usual sulfonamide dosage can keep the plasma sulfonamide level in the usual range in patients with poor renal function, it cannot prevent the plasma levels of acetylsulfonamide from rising to higher than usual levels. Adam and Dawborn observed high acetylsulfonamide levels in all 4 patients with very poor renal function in their study and correlated this with drug-related nausea and vomiting in three of the patients (8).

Meperidine is normally metabolized to normeperidine which may then be either excreted in the urine or further metabolized. Normeperidine has been shown in animals to have less analgesic potency but more convulsant potency than meperidine. Patients with renal

failure given meperidine for post-transplantation analgesia have marked accumulation of normeperidine after a few doses of the parent drug. Two patients with poor renal function receiving meperidine and having signs and symptoms of central nervous system irritability had high normeperidine levels. The meperidine was stopped, and the central nervous system irritability subsided. This decline in CNS irritability seemed to parallel the fall of normeperidine levels in the one patient in whom it was measured (9).

Procainamide is excreted unchanged or acetylated to N-acetylprocainamide which is then eliminated from the body by urinary excretion. N-Acetylprocainamide has an action on the heart that is similar to procainamide (10-12). Patients with renal failure receiving procainamide at dosages appropriately reduced to correct for the slower than normal elimination of procainamide still had marked accumulation of N-acetylprocainamide. The intensity of effect observed, both therapeutic and toxic, was clearly related to this metabolite accumulation as well as the procainamide itself (13).

These examples demonstrate that clofibrate, allopurinol, sulfonamides, meperidine, and procainamide are biotransformed to active metabolites that accumulate and produce effects in patients with poor renal function. A great many other drugs are known to have

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