

Combination analgesic-induced kidney disease: the Australian experience.

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Analgesic nephropathy is a unique drug-induced kidney disease characterized pathologically by renal papillary necrosis and chronic interstitial nephritis, and is the result of excessive consumption of combination antipyretic analgesics. The clinical features of the disorder relate mainly to the papillary necrosis, renal colic, and obstructive uropathy and the development of chronic renal failure in a small percentage of patients. There are significant geographic variations in the clinical features that may be related to the differing combinations of analgesics. The pathogenesis of the disease is in part related to the kidneys' ability to concentrate drugs in the papillae. The following sequence of events presents a plausible explanation for the evolution of the disease. If a combination of phenacetin and aspirin is ingested, the following steps occur. Phenacetin is converted in the gut and liver to acetaminophen by first-pass metabolism. Acetaminophen is then taken up by the kidney and excreted. During its excretion, acetaminophen becomes concentrated in the papillae of the kidney during physiologic degrees of antidiuresis, the concentration being up to five times the intracellular concentration of other tissues. Acetaminophen undergoes oxidative metabolism by prostaglandin H synthase to a reactive quinoneimine that is conjugated to glutathione. If acetaminophen is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. If the acetaminophen is ingested with aspirin, the aspirin is converted to salicylate and salicylate becomes highly concentrated in both the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. The mechanism is not completely understood; however, the inhibition of the production of NADPH via the pentose shunt is a possible explanation. With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae.

