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Probenecid

Updated: January 22, 2014.

OVERVIEW

Introduction

Probenecid is a uricosuric agent used for the treatment of gout usually in combination with other agents. Probenecid has been associated with minor serum aminotransferase elevations and very rarely with hypersensitivity reactions which, even more rarely, can be accompanied by acute liver injury.

Background

Probenecid (proe ben' e sid) is a sulfonamide derivative that acts as an inhibitor of inorganic acid transport in the distal renal tubule, causing blockage of reabsorption of uric acid. Therapy leads to lowering of serum uric acid levels within a few weeks, and chronic therapy has been shown to decrease uric acid levels and to decrease acute gouty attacks. Probenecid also inhibits the excretion of penicillin and other drugs and has been used as an adjunct to penicillin therapy to increase plasma drug levels. Probenecid was approved for use in the United States in 1951 and is still used for therapy and prevention of gout and hyperuricemia. Probenecid is available in tablets of 500 mg in several generic forms and under brand names such as Benemid and Benuryl, as well as in fixed combinations with colchicine. The recommended initial dose for gout is 250 to 500 mg twice a day, which can be increased to 2 g daily based upon target levels of uric acid. Probenecid is typically used in combination with other agents for gout, such as colchicine. Common side effects include headache, gastrointestinal upset, hypersensitivity reactions and transient worsening of gout.

Probenecid is also used in combination with penicillin and penicillin derivatives (such as ampicillin and nafcillin) to prolong their plasma half-life and increase serum concentrations. The typical dose for this effect is 1 g daily. Importantly, however, probenecid has similar effects on many other medications, inhibiting the tubular secretion and increasing serum concentrations of drugs such as acetaminophen, naproxen, indomethacin, ketoprofen, lorazepman and rifampcin. Thus, patients taking probenecid should be cautioned about use of other medications.

Hepatotoxicity

There are no reports on the frequency of liver test abnormalities during probenecid therapy, but they are probably rare as the drug is largely secreted unchanged in the urine. A single case report of a severe hypersensitivity reaction from probenecid and rechallenge with severe recurrence of jaundice was reported over 50 years ago.

Mechanism of Injury

The mechanism of probenecid hepatotoxicity is probably hypersensitivity. Most cases of hypersensitivity to probenecid are marked by skin rash alone, without liver damage.

Outcome and Management

Chronic hepatitis and vanishing bile duct syndrome have not been reported from probenecid therapy. Hypersensitivity reactions (largely rash and urticaria) to probenecid can occur and rechallenge should be avoided as the single case of severe liver injury reported was in a patient who was retreated with probenecid after a prolonged hypersensitivity reaction to a previous exposure.

Drug Class: Antigout Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Probenecid – Generic, Benemid®

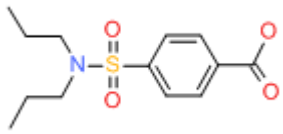
DRUG CLASS

Antigout Agents/Gout Suppressants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Probenecid	57-66-9	C13-H19-N-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 22 January 2014

Zimmerman HJ. Drugs used to treat gout. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 543-4.

(Textbook of hepatotoxicity published in 1999; mentions that probenecid has effects on indocyanine green [ICG] and sulfobromophthalein [BSP] excretion, but rarely causes liver injury; despite years of use only a single case report of severe hypersensitivity with jaundice has been published).

Grosser T, Smyth E, FitzGerald GA. Pharmacology of gout. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 994-1004.

(Textbook of pharmacology and therapeutics).

Reynolds ES, Schlant RC, Gonick HC, Dammin GJ. Fatal massive necrosis of the liver as a manifestation of hypersensitivity to probenecid. N Engl J Med 1957; 256: 592-6. PubMed PMID: 13451901.

(57 year old man developed fever, rash, eosinophilia and jaundice 2 days after starting probenecid, with slow recovery upon withdrawal and recurrence of fever and jaundice upon restarting, whereupon drug was continued for 10 days when he was admitted with acute liver failure; autopsy showed massive necrosis and portal inflammation without fibrosis).

Hillecke N. Acute anaphylactoid reaction to probenecid. JAMA 1965; 193: 740. PubMed PMID: 14328478.

(61 year old man developed anaphylaxis after single dose of colchicine-probenecid with leukemoid reaction, hypotension and fever, recovering within a week; rechallenge with probenecid without colchicine resulted in recurrence of anaphylaxis [bilirubin not given, AST 80 U/L]).

Vogin EE, Scott W, Boyd J, Bear WT, Mattis PA. Effect of probenecid on indocyanine green clearance. J Pharmacol Exper Ther 1966; 152: 509-15. PubMed PMID: 5922315.

(In beagles, probenecid caused a reversible and dose related inhibition of indocyanine green excretion and increase in bile flow, probably due to its known effects on membrane transport).