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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Rasburicase. [Updated 2018 May 21].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Rasburicase

Updated: May 21, 2018.

OVERVIEW

Introduction

Rasburicase is a parenterally administered, recombinant urate oxidase that is used in combination with xanthine oxidase inhibitors in the therapy of severe hyperuricemia due to tumor lysis syndrome after initiation of cancer chemotherapy in treatment of malignant diseases. Rasburicase has been associated with serum enzyme elevations during therapy and to rare instances of hypersensitivity reactions that can be accompanied by liver injury.

Background

Rasburicase (ras bure' i kase) is a DNA recombinant urate oxidase derived from the fungus Aspergillus flavus. Urate oxidase is an enzyme that catalyzes the metabolism of uric acid to allantoin, which is an inert and inactive molecule that, unlike uric acid, is rapidly excreted in the urine. Infusions of rasburicase lower serum uric acid levels by hastening its excretion and have been shown to be effective in rapidly lowering uric acid levels in patients with tumor lysis syndrome after initiation of cancer chemotherapy. Rasburicase was approved for use in the treatment and prevention of hyperuricemia due to tumor lysis syndrome after cancer chemotherapy in the United States in 2002. Rasburicase is available as a powder for reconstitution in vials of 1.5 and 7.5 mg under the brand name Elitek. The recommended dose is 0.2 mg/kg given intravenously once daily for up to 5 days. Common side effects of rasburicase include nausea, vomiting, fever, peripheral edema, anxiety, headache, abdominal pain, constipation and diarrhea. Severe adverse reactions can include local infusion reactions, hypersensitivity reactions, anaphylaxis and hemolytic anemia with methemoglobinemia in patients with G6PD deficiency.

Hepatotoxicity

In prelicensure clinical trials, serum enzyme elevations were not uncommon (4% to 24%) and were occasionally above 5 times ULN (<1%) during rasburicase therapy. These elevations generally resolved rapidly once rasburicase was discontinued. Because patients receiving rasburicase were typically receiving cancer chemotherapy and other drugs for hyperuricemia such as allopurinol, the liver enzyme elevations observed could not always be attributed to rasburicase. Subsequent to its approval and more wide scale use, rasburicase has been linked to hypersensivity reactions that may be accompanied by marked serum ALT and AST elevations with mild jaundice. In at least one instance, these abnormalities recurred upon re-exposure to rasburicase. These reactions generally arise within hours of administration of rasburicase and resolve rapidly with its discontinuation with or without the use of corticosteroids. Rasburicase has not been linked to instances of acute

liver failure or chronic liver injury. Thus, rasburicase is a well-known cause of hypersensivity reactions, some of which may be accompanied by hepatic injury.

Likelihood score: D (possible cause of clinically apparent liver injury accompanying hypersensitivity reactions).

Mechanism of Injury

Rasburicase is a recombinant protein and is metabolized to amino acids by serum and tissue proteases, and is unlikely to have any direct hepatotoxic potential. The marked liver test abnormalities noted in some patients treated with rasburicase were associated with other features of hypersensitivity.

Outcome and Management

The serum enzyme elevations during rasburicase therapy are usually mild-to-moderate in severity and rarely require dose modification. Hypersensitivity reactions to rasburicase can be accompanied by mild-to-moderate liver injury. Therapy should be directed at the signs and symptoms of hypersensitivity rather than liver injury itself.

Drug Class: Antigout Agents

CASE REPORT

Case 1. Hypersensitivity reaction with hepatic involvement caused by rasburicase.

[Modified from: Viel S, Pescarmona R, Belot A, Nosbaum A, Lombard C, Walzer T, Bérard F. A case of type 2 hypersensitivity to rasburicase diagnosed with a natural killer cell activation assay. Front Immunol 2018; 9: 110. PubMed Citation]

A 62 year old man with leukemia developed fever and liver test abnormalities during his fourth course of chemotherapy with pentostatin and tumor lysis syndrome prophylaxis using allopurinol and rasburicase. His white blood cell counts were elevated and he was admitted for therapy of suspected sepsis. His medications were stopped. He had no previous history of liver disease, alcohol abuse or risk factors for viral hepatitis. Laboratory testing showed marked elevations in serum aminotransferase levels (ALT 1102 U/L, AST 773 U/L and LDH 1339 U/L with mild hyperbilirubinemia (3.3 mg/dL) and decrease in the prothrombin index (46%) (Table). His condition improved rapidly and he was discharged. Two months later he was evaluated for hypersensitivity to rasburicase with skin tests. An hour after the single dose of rasburicase (5.5 mg), he developed fever (39.5 ^{o}C) and liver tests were again raised.

Key Points

Medication:	Rasburicase
Pattern:	Hepatocellular
Severity:	3+ (jaundice, hospitalization)
Latency:	4 months
Recovery:	Within 2 months
Other medications:	Allopurinol, pentostatin

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	GGT (U/L)	Bilirubin (mg/dL)	Other

Table continued from previous page.

4 months	0	1102	307	3.3	Fever and leukocytosis
	2 days	863	225	5.9	Prothrombin ratio [PR] 46%
	Discharged, chemotherapy withheld				
6 months	2 months	43	22	0.4	PR 98%
	Skin tested with rasburicase				
	3 hours	73	99	1.0	PR 90%
	6 hours	257	202	1.5	PR 77%
	24 hours	220	171		PR 54%
Normal Values		**<55**	**<64**	**<1.2**	

Comment

This patient presented with a hypersensitivity reaction with hepatic involvement resulting in mild jaundice, but a self-limited course. He was later evaluated with skin testing for drug allergy in an attempt to show whether the reaction was due to rasburicase versus allopurinol or pentostatin. After a single intradermal injection of rasburicase, he developed fever followed by elevations in serum aminotransferase levels and total bilirubin. Thus, the role of rasburicase in the reaction was fairly convincingly documented.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rasburicase – Elitek®

DRUG CLASS

Antigout Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Rasburicase	134774-45-1	Protein	Complex Polypeptide

ANNOTATED BIBLIOGRAPHY

References updated: 21 May 2018

Zimmerman HJ. Drugs used to treat gout. Drugs used to treat rheumatic and musculospastic disease. 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 and before the availability of rasburicase).

Grosser T, Smyth E, FitzGerald GA. Pharmacotherapy of gout. Anti-inflammatory, antipyretic and analgesic agents; pharmacotherapy 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. 994-1000.

(Textbook of pharmacology and therapeutics).

Pui CH, Jeha S, Irwin D, Camitta B. Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. Leukemia 2001; 15: 1505-9. PubMed PMID: 11587206.

(Among 173 children and 72 adults receiving cancer chemotherapy who were treated with rasburicase, all had a rapid decline in serum uric acid, usually into the normal range and side effects included vomiting, itching, urticarial, rash, fever, headache and myalgia).

Rasburicase (Elitek) for hyperuricemia. Med Lett Drugs Ther 2002; 44 (1143): 96-7. PubMed PMID: 12432325.

(Concise review of the indications, pharmacology, clinical efficacy, side effects and costs of rasburicase shortly after its approval for use in the US mentions anaphylactic reactions, but not ALT elevations or liver injury).

Coiffier B, Mounier N, Bologna S, Fermé C, Tilly H, Sonet A, Christian B, et al.; Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 study. J Clin Oncol 2003; 21: 4402-6. PubMed PMID: 14581437.

(Among 100 patients with lymphoma undergoing chemotherapy who received rasburicase infusions, uric acid levels were controlled in all patients and none required dialysis during chemotherapy; therapy was stopped early in 3 patients for ALT elevations above 5 times ULN, which rapidly resolved).

Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, Camitta B, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia 2005; 19: 34-8. PubMed PMID: 15510203.

(Among 658 children and 338 adults with malignancies who received rasburicase at the time of chemotherapy, uric acid levels fell and the only nonresponders had discontinued therapy early; side effects were rare but included hemolytic anemia due to G6PD deficiency, renal insufficiency, hypersensitivity reactions, but only one patient had ALT elevations above 5 times ULN).

Kikuchi A, Kigasawa H, Tsurusawa M, Kawa K, Kikuta A, Tsuchida M, Nagatoshi Y, et al. A study of rasburicase for the management of hyperuricemia in pediatric patients with newly diagnosed hematologic malignancies at high risk for tumor lysis syndrome. Int J Hematol 2009; 90: 492-500. PubMed PMID: 19701676.

(Among 30 children with hematologic malignancies given rasburicase for 5 days during initial chemotherapy, serum uric acid levels remained below 6.5 mg/dL in all except one patient; ALT elevations above 5 times ULN occurred in 70% of children, but were attributed to the chemotherapy rather than rasburicase).

Ishizawa K, Ogura M, Hamaguchi M, Hotta T, Ohnishi K, Sasaki T, Sakamaki H, et al. Safety and efficacy of rasburicase (SR29142) in a Japanese phase II study. Cancer Sci. 2009; 100 (2): 357-62. PubMed PMID: 19076979.

(Among 50 patients with lymphoma or leukemia treated with rasburicase for 5 days starting after the first dose of chemotherapy, serum uric acid levels fell and were less than 7.5 mg/dL in all, while side effects included ALT elevations in 24% [above 5 times ULN in 4%], which resolved after therapy in all and hypersensitivity reactions in 3 patients [6%]).

Cortes J, Moore JO, Maziarz RT, Wetzler M, Craig M, Matous J, Luger S, et al. Control of plasma uric acid in adults at risk for tumor Lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone--results of a multicenter phase III study. J Clin Oncol 2010; 28: 4207-13. PubMed PMID: 20713865.

(Among 273 children with hematologic malignancies treated with rasburicase, allopurinol or both for 5 days at the start of chemotherapy, uric acid responses were more frequent and rapid with rasburicase, and hypersensitivity reactions arose in 4% and liver test abnormalities in 1% of rasburicase recipients).

Galardy PJ, Hochberg J, Perkins SL, Harrison L, Goldman S, Cairo MS. Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: a Children's Oncology Group Report. Br J Haematol 2013; 163: 365-72. PubMed PMID: 24032600.

(Among 76 children undergoing cytoreductive therapy in preparation of hematopoietic cell transplantation who received rasburicase to prevent tumor lysis syndrome, 3 patients developed hypersensitivity symptoms, but there were no serious adverse events attributed to the rasburicase therapy).

Digumarti R, Sinha S, Nirni SS, Patil SG, Pedapenki RM. Efficacy of rasburicase (recombinant urate oxidase) in the prevention and treatment of malignancy-associated hyperuricemia: an Indian experience. Indian J Cancer 2014; 51: 180-3. PubMed PMID: 25104205.

(Among 88 patients at high risk of tumor lysis syndrome from chemotherapy who received rasburicase, uric acid levels decreased by an average of 75% and there were "no significant changes in … biochemical parameters from baseline" and no serious adverse events thought to be related to rasburicase).

Drugs for gout. Med Lett Drugs Ther 2014; 56 (1438): 22-4. PubMed PMID: 24791281.

(Update on medications for gout discusses the urate lowering agents allopurinol, febuxostat, probenecid and pegloticase, but not lesinurad or rasburicase).

Baldo BA. Enzymes approved for human therapy: indications, mechanisms and adverse effects. BioDrugs 2015; 29: 31-55. PubMed PMID: 25648140.

(Review of enzymes that are approved for use in the US including those used for enzyme replacement therapy [for Gaucher, Fabry, Pompe, and several MPS] as well as those for specific diseases [dornase for cystic fibrosis, alteplase for myocardial infarction and stoke, L-asparaginase for cancer and pegloticase and rasburicase for hyperuricemia and gout]; no mention of ALT elevations or hepatotoxicity except for L-asparaginase).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury in the US collected between 2004 and 2012, 8 cases were attributed to drugs used for gout [allopurinol in 7 and febuxostat in 1], but no cases were attributed to pegloticase or rasburicase).

Tamura K, Kawai Y, Kiguchi T, Okamoto M, Kaneko M, Maemondo M, Gemba K, et al. Efficacy and safety of febuxostat for prevention of tumor lysis syndrome in patients with malignant tumors receiving chemotherapy: a phase III, randomized, multi-center trial comparing febuxostat and allopurinol. Int J Clin Oncol 2016; 21 (5): 996-1003. PubMed PMID: 27017611.

(Among 100 patients with malignancies undergoing chemotherapy who were treated prophylactically with either allopurinol or febuxostat, the rate and degree of uric acid decline and side effects were similar in the two groups, and 1 patient in each group had serum ALT elevations [both were less than 3 times ULN]).

Viel S, Pescarmona R, Belot A, Nosbaum A, Lombard C, Walzer T, Bérard F. A case of type 2 hypersensitivity to rasburicase diagnosed with a natural killer cell activation assay. Front Immunol 2018; 9: 110. PubMed PMID: 29434608.

(62 year old man developed fever and jaundice during a 4th course of chemotherapy while receiving allopurinol and rasburicase [bilirubin 3.3 mg/dL, ALT 1162 U/L, GGT 307 U/L, leukocytosis], which rapidly resolved on stopping but recurred several months later after a skin test challenge with rasburicase [bilirubin 1.5 mg/dL, ALT 257 U/L, GGT 202 U/L], resolving rapidly).