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ORIGINAL RESEARCH ARTICLE

# Risk of Anaphylaxis with Repeated Courses of Rasburicase: A Research on Adverse Drug Events and Reports (RADAR) Project

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**Abstract**

*Background* Rasburicase, a recombinant urate oxidase, is used to rapidly metabolize uric acid in patients with hyperuricaemia. Rasburicase is an immunogenic therapeutic protein, which has been shown to elicit antibody response in 64 % of healthy volunteers within 1–6 weeks after the initial course, with persistent antibodies for over 1 year. Drug labelling indicates that anaphylaxis rarely occurs (in <1 % of patients) after a single course of therapy with rasburicase, but there are no data available on the incidence of anaphylaxis in patients receiving a subsequent rasburicase course.

*Objective* The objective of this study was to determine the incidence of anaphylaxis after multiple treatment courses of rasburicase.

*Methods* A retrospective chart review was performed on 97 consecutively treated patients who received repeated courses of rasburicase for hyperuricaemia.

*Results* None of the 97 patients who were reviewed experienced anaphylaxis during the first rasburicase course; however, six patients (6.2 %) experienced anaphylaxis during a subsequent rasburicase treatment course ($p = 0.03$).

*Conclusion* Anaphylaxis after a second course of rasburicase appears to occur more frequently than described in the US Food and Drug Administration-approved package insert for initial treatment courses. Given the serious nature of anaphylactic events, caution is advised when administering repeated courses of rasburicase.

**Key Points**

Anaphylaxis after a second course of rasburicase appears to occur more frequently than described in the US Food and Drug Administration-approved package insert for initial treatment courses.

Given the serious nature of anaphylactic events, caution is advised when administering repeated courses of rasburicase.

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## 1 Introduction

Hyperuricaemia, a result of rapid cell turnover and release of deoxyribonucleic acid (DNA) breakdown products, is a serious complication that occurs in patients with high-grade malignancies receiving anti-cancer therapy [1]. Rasburicase, a recombinant urate oxidase, converts uric acid into its more soluble and inactive metabolite, allantoin, and has been approved by the US Food and Drug Administration (FDA) for prevention of elevated plasma uric acid levels in these patients [2]. At the approved dose, rasburicase reduces serum uric acid to undetectable levels within 4 hours and maintains them more efficiently than allopurinol [1, 3]. The manufacturer's prescribing information recommends a single course of treatment, which consists of once-daily weight-based infusions for up to 5 days [2]. Patients who receive rasburicase during their initial course of chemotherapy and subsequently relapse frequently receive salvage therapeutic regimens, which may place them at risk of developing recurrent hyperuricaemia. Rasburicase's safety has not been ascertained for dosing beyond 5 days, because of insufficient data. The FDA has issued boxed warnings for rasburicase because of its association with haemolysis, methaemoglobinaemia and severe hypersensitivity reactions, including anaphylaxis. In the drug packet insert, these adverse events are reported to occur at an incidence of $<1$ % [2].

Limited information is available about the nature of rasburicase's immunogenicity. Historically, urate oxidase isolated from *Aspergillus flavous* was used for treatment of hyperuricaemia, with reported acute hypersensitivity reactions occurring in roughly 5 % of patients [4]. Rasburicase is a recombinant form of urate oxidase derived from genetically modified *Saccharomyces cerevisiae*, which appears to be less immunogenic [2, 4]. No studies published to date have investigated the correlation between anti-rasburicase immunoglobulin (Ig) formation and adverse allergic events. Currently available assay methods for detecting anti-rasburicase antibodies (Ras antibodies) are not standardized, making it difficult to compare results between studies [2, 5]. The Research on Adverse Drug Events and Reports (RADAR) project is a post-marketing surveillance programme, which investigates serious adverse reactions to FDA-approved drugs and devices [6, 7]. Through a retrospective chart review, our purpose was to assess the incidence and severity of anaphylactic reactions in patients receiving more than one therapeutic course of rasburicase, and to compare the rate of anaphylaxis between the first course and subsequent courses of therapy separated by at least 21 days.

## 2 Methods

A retrospective review of Northwestern Memorial Hospital's electronic medical records identified patients from January 2004 to January 2012 with haematological malignancies who had received repeated courses of rasburicase for treatment of hyperuricaemia. All patients had received an initial, single, non-weight-based dose of rasburicase (3 or 6 mg) and one or more subsequent doses a minimum of 21 days after the initial dose [8, 9]. The decision to use rasburicase and the chosen rasburicase dose were based upon the attending physician's discretion. The diagnosis of anaphylaxis was determined by documentation of an anaphylactic reaction in the medical record with a report of the event, including descriptors such as hypersensitivity, angioedema, hypoxia, airway compromise or respiratory failure. Data extracted from the medical record for each evaluable subject included the type of haematological disorder, total number of doses of rasburicase, dose of rasburicase used in each course, dates of first and subsequent exposure to rasburicase, date and time of the anaphylactic event, administration time of the dose of rasburicase that preceded anaphylaxis, description of the anaphylactic event and outcome, and other comorbid conditions. Patients were not tested for glucose-6-phosphate dehydrogenase deficiency or methaemoglobinaemia. This study was approved by the Northwestern University Institutional Review Board (IRB). SPSS® Statistics version 18 software (IBM, Armonk, NY, USA) was used to perform chi-squared tests, Fisher's exact tests and paired *t* tests.

## 3 Results

Ninety-seven patients met the criteria for inclusion in the study (Table 1). Of these 97 patients, six patients (6.2 %) experienced anaphylaxis following a subsequent administration of rasburicase for recurrent hyperuricaemia (Table 2), as compared with no occurrences of anaphylaxis after rasburicase was administered for the first episode of hyperuricaemia ($p = 0.03$). Among the myeloma patients who reacted to rasburicase, only one patient had received high-dose corticosteroids (methylprednisone 125 mg once) within 14 days of rasburicase treatment. The mean time from the initial rasburicase exposure to the second rasburicase exposure that was accompanied by an anaphylactic event was 257 days (8.5 months). In five of the six patients, anaphylaxis was experienced within 2 h of the second drug exposure. The calculated number needed to harm for a repeated course of rasburicase is 17 (95 % confidence interval 9.1–71.9). Among the five myeloma patients who reacted to rasburicase, there was no

**Table 1** Patient baseline demographic characteristics

| Characteristic | With anaphylaxis | Without anaphylaxis | *p* value |
|---|---|---|---|
| *n* | 6 | 91 | |
| Age [years; mean (range)] | 48.5 (43–55) | 57 (21–87) | 0.12 |
| Sex: male [*n* (%)] | 4 (66.6) | 65 (71.4) | 0.81 |
| Weight [kg; mean (range)] | 86.85 (55.6–124.6) | 85.7 (47.3–164) | 0.92 |
| Diagnosis [*n* (%)] | | | |
| Acute leukaemia | 0 (0) | 22 (24.2) | 0.33 |
| Chronic leukaemia | 0 (0) | 6 (6.6) | 1.0 |
| Multiple myeloma | 5 (83.3) | 41 (45.0) | 0.09 |
| Other | 1 (16.7) | 22 (24.2) | 1.0 |
| Baseline uric acid [mg/dL; mean (range)] | 8.85 (7.5–10.2) | 9.44 (5.1–18.1) | 0.47 |
| Baseline serum creatinine [mg/dL; mean (range)] | 2.56 (1.33–5.28) | 2.12 (0.67–8.66) | 0.45 |
| Tumour lysis syndrome [*n* (%)] | 1 (16.6) | 34 (37.4) | 0.41 |
| Lactate dehydrogenase [IU/L; mean (range)] | 646 (174–2109) | 434 (83–2481) | 0.32 |
| Rasburicase dose [mg; mean (range)] | 3.5 (3–6) | 3.07 (3–6) | 0.96 |
| Rasburicase dose [mg/kg; mean (range)] | 0.042 (0.024–0.064) | 0.038 (0.018–0.085) | 0.32 |

**Table 2** Cases of anaphylaxis ($n = 6$) associated with administration of repeated courses of rasburicase ($n = 97$)

| Diagnosis | Total number of courses | Total rasburicase exposure (mg) | Comorbid conditions prior to rasburicase administration | Time between first course and anaphylaxis (days) | Time between rasburicase administration and anaphylaxis (min) | Intensive care unit admission | Intubation and cardiac arrest | Death |
|---|---|---|---|---|---|---|---|---|
| Multiple myeloma | 2 | 6 | End-stage renal disease, pancytopenia, fever, hypertension, mucositis, kyphoscoliosis | 22 | 112 | Yes | Yes | No |
| Chronic myeloproliferative disorder | 2 | 6 | Asthma, chronic kidney disease, deep vein thrombosis, chronic pain, insomnia | 21 | 337 | Yes | Yes | Yes |
| Multiple myeloma | 2 | 9 | Pneumonia, acute kidney injury, urinary tract infection | 695 | 40 | No | No | No |
| Multiple myeloma | 3 | 12 | Acute kidney injury, hypotension, pneumonia, urinary tract infection | 319 | 10 | No | No | No |
| Multiple myeloma | 2 | 6 | Decompensated congestive heart failure, peripheral neuropathy, chronic kidney disease | 150 | <10 | No | No | No |
| Multiple myeloma | 4 | 18 | Hypertension, pancytopenia, acute kidney injury, type 2 diabetes mellitus, anxiety, depression | 335 | 59 | Yes | No | No |

identifiable pattern of underlying immunoglobulin class abnormality (kappa light chain $n = 2$, lambda light chain $n = 1$, IgA $n = 1$ and 1gG $n = 1$).

All six anaphylaxis patients had compromised renal function prior to the second course of rasburicase. There was no evidence of haemolysis in any of the patients who

experienced anaphylaxis. Anaphylaxis occurred significantly more often in patients with multiple myeloma ($p < 0.004$). Two patients who had laboratory tumour lysis syndrome at the time of anaphylaxis developed clinical tumour lysis syndrome, as defined by the Cairo–Bishop criteria [10]. No neurological events were noted. Three patients were transferred to the intensive care unit, two of whom required intubation. Two patients subsequently experienced cardiac arrest, one of whom died.

## 4 Discussion

The incidence of anaphylaxis after a repeated course of rasburicase in our study population was 6 %, compared with an incidence of <1 % reported in the drug's package insert. This finding suggests that the incidence of anaphylaxis with repeated courses of rasburicase may be significantly higher than the incidence reported by the manufacturer for the initial treatment course. This study population exclusively comprised patients receiving reduced doses of rasburicase. The incidence of anaphylaxis could be higher in patients receiving the recommended weight-based dose, which tends to be much higher.

Hyperuricaemia occurs when uric acid generation from chemotherapy-associated cell lysis exceeds the kidney's ability to excrete uric acid. While this occurs most frequently in patients with high-grade malignancies receiving aggressive chemotherapy regimens, it may also be seen in patients treated for indolent haematological malignancies, such as chronic lymphocytic leukaemia or multiple myeloma with or without pre-existing renal dysfunction [1]. Hyperuricaemia and increased urinary uric acid excretion result in acidification of the urine, a further reduction in uric acid solubility and crystallization. Urate crystals obstruct renal tubules and promote local granulomatous inflammation [11, 12]. In addition to urate crystal formation, uric acid induces acute kidney injury by stimulating renal vasoconstriction and reducing renal perfusion [11, 12], promoting pro-inflammatory and pro-oxidative mediators, causing injury to renal microvasculature and modifying renal auto-regulatory mechanisms [12]. Hyperuricaemia is a serious consequence of anti-cancer therapies, and effective prevention with urate-lowering agents may help to prevent this complication. However, conventional urate-lowering agents, such as allopurinol or probenecid, are not as effective in reducing pre-existing elevated serum uric acid levels as rasburicase, especially in the setting of acute kidney injury [1]. The role of rasburicase is crucial in this acute setting. Although rasburicase is generally well tolerated, the results of the present case series suggest that immediate hypersensitivity reactions occur more frequently after prior exposure to rasburicase, requiring physicians to be more cautious when administering rasburicase to patients who have previously received this drug.

The ability of rasburicase to elicit hypersensitivity reactions is attributed to its immunogenicity, or its capability of producing an immune response [13, 14]. All recombinant drugs are potentially immunogenic, and this property presents certain challenges. Antibody formation towards therapeutic proteins can result in reduced efficacy of the drug, neutralization of endogenous protein activity or hypersensitivity reactions, including anaphylaxis [4, 13]. It has been suggested that these hypersensitivity reactions are caused by IgG and IgE antibodies, and they more frequently occur with repeated administration of protein therapies derived from non-human sources [4]. The immunogenicity of a therapeutic protein is influenced by product-related factors, such as the protein structure, antigenic epitope exposure, the amount of glycosylation and downstream drug processing (i.e. impurities and contaminants). Patient-related factors that can affect immunogenicity include the genetic background, underlying liver and renal disease, and auto-immune disease. In this review, three of the six patients experiencing anaphylaxis had pre-existing chronic kidney disease and none of the six patients had liver disease or auto-immune disease. In general, the risk of immunogenicity is increased with higher drug doses and with a longer duration of treatment [15]. The route of drug administration has also been reported to influence drug immunogenicity; subcutaneous and intramuscular administration may be more likely to evoke an immune response than intravenous administration [15].

The current understanding of anti-rasburicase antibody formation is limited. In 260 rasburicase-naïve adults with haematological malignancies who were given a 5-day course of rasburicase, 18 % were positive for anti-rasburicase IgG, 8 % were positive for anti-rasburicase neutralizing IgG, and 6 % were positive for anti-rasburicase IgE from day 14 up to 24 months after rasburicase administration. In another trial, 11 % of 218 paediatric patients with haematological malignancies had developed antibodies by 28 days after the initial rasburicase dose [2]. According to the FDA product approval information, in a study of 28 healthy volunteers given either one dose or five daily doses of rasburicase, 61 % developed binding antibodies to rasburicase and 64 % developed neutralizing antibodies within 1–6 weeks. Antibodies persisted in two of these subjects for 333 and 494 days, respectively [16].

The underlying mechanism of anaphylaxis with repeated courses of rasburicase is unknown. The yeast *S. cerevisiae* that is used to produce rasburicase is widely used in baking, brewing and winemaking, and it has been associated with auto-immune diseases of the gut. One could speculate that a percentage of patients in our study had pre-existing *S.*

*cerevisiae* antibodies, which reacted with rasburicase. In our study population, the timing of anaphylaxis after rasburicase administration ranged from immediate onset to onset after a few hours, and the time between the first rasburicase exposure and anaphylaxis was as long as 23 months. To date, no studies have assessed the correlation between antibody formation, timing of courses of rasburicase administration and anaphylactic reactions.

Given the serious nature of anaphylactic events, practitioners should use caution when administering repeated courses of rasburicase. At Northwestern Memorial Hospital, new institutional guidelines have been enacted so that when a patient requires more than one course of rasburicase separated by at least 7 days, pharmacists, prescribers and nursing staff are notified of the potential for anaphylaxis, the need to consider pre-medication with antihistamines and corticosteroids, and the need to keep epinephrine at the bedside.

## 5 Study Limitations

This study was limited by its single-centre, retrospective nature, making it difficult to generalize its results to a broader population. Further inquiry into the process behind rasburicase-induced anaphylaxis is limited by the lack of commercially-available, uniform assays for measuring these antibodies [5].

## 6 Conclusion

The incidence of anaphylaxis associated with repeated courses of rasburicase is significantly greater than after an initial course. Future assessments of the safety of repeated courses of rasburicase should be evaluated in hospital-based programmes and with thorough post-marketing observation. Further research aimed at understanding anti-rasburicase antibody production and the mechanism of anaphylaxis with repeated rasburicase courses could yield useful information to improve the safety of administering multiple courses of rasburicase.

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