

Desensitization to 5-Fluorouracil

Thomas Eppinger, M.D., Ph.D., and Kirk Sperber, M.D.

ABSTRACT

Anaphylactic reactions to 5-fluorouracil (5-FU) are uncommon. We report a 40-year-old female with adenocarcinoma of the ovary who had two reactions immediately after being infused with 5-FU. The second reaction occurred despite prophylaxis with steroids and antihistamines. The patient was positive to 5-FU on puncture skin testing even though there was no previous exposure to the drug. We successfully desensitized her to 5-FU using a continuous intravenous protocol with sequential increments in the fusion rates and drug concentrations. This desensitization method may be useful to manage systemic reactions to 5-FU and other drugs. (Allergy and Asthma Proc 20:189–191, 1999)

5-Fluorouracil (5-FU) is an established chemotherapeutic agent used to treat many different types of malignancies including carcinoma of the colon, rectum, breast, stomach, pancreas, and ovary.¹ 5-FU is an anti-metabolite that blocks the methylation reaction of deoxyuridylic acid and thymidylallic acid so that it interferes with DNA and to a lesser extent RNA formation, being especially toxic to rapidly growing malignant cells.² It has a half life of approximately 16 minutes after intravenous administration and has a narrow safety margin.² This agent also has a number of side effects including nausea, vomiting, diarrhea, leukopenia, and thrombocytopenia and other less common side effects including stomatitis, skin pigmentation, hepatic, renal and central nervous system toxicity, as well as allergic reactions.³ There are scattered reports of anaphylactic reactions occurring after the intravenous administration of 5-FU, but overall the risk of allergic reactions and anaphylaxis is low. Here, we report a patient with no prior exposure to 5-FU who had two immediate reactions to the drug, positive allergy skin tests, and was successfully desensitized

using a modified intravenous protocol. To our knowledge there have been only three other cases reported, and in none of these previous cases was the patient successfully re-administered 5-FU.^{4–6}

CASE REPORT

The patient, a 40-year-old 60 kilogram Caucasian female previously in good health, complained of right lower quadrant abdominal pain in November 1997. She underwent an exploratory laparotomy and was found to have adenocarcinoma of the ovary with involvement of the appendix and 2 of 13 abdominal lymph nodes positive for tumor. After surgical resection of the ovary and appendix, she received a chemotherapeutic regime that included 5-FU. Five minutes after the first intravenous administration of 5-FU (6 mg/Kg), she immediately experienced chest tightness, shortness of breath, lip swelling, flushing, and diffuse pruritus. The infusion was stopped and she improved with treatment that included diphenhydramine 50 mg intramuscularly and epinephrine (1:1000) (0.3 cc) subcutaneously. There was no prior exposure to 5-FU, and the only notable allergy history was of a seasonal rhinitis and no adverse reactions to other drugs. Since she required 5-FU for the chemotherapy, she was pretreated with 150 mg of prednisolone orally in three divided doses over 13 hours and diphenhydramine 25 mg intramuscularly 1 hour before the infusion. Despite the pretreatment regimen, she had a second systemic reaction immediately after receiving an intravenous test dose of 5-FU (1 mg) consisting of pruritus, chest tightness, and flushing, which again resolved with diphenhydramine and epinephrine treatment after the infusion was stopped.

She was then skin tested for the presence of an IgE antibody to 5-FU (Roche, Nutley, NJ) by puncture skin testing using serial dilutions of the drug (0.001–1 mg/mL). Both the wheal and flare responses were measured in millimeters as the average of the largest diameter and the perpendicular to the midpoint of the diameter. A reaction was considered positive if the wheal was 3 to 5 mm greater than the negative diluent control and/or a flare of 10 mm or greater. The patient had a positive reaction (D_{50}) to 5-FU at a concentration of 0.01 mg/mL (wheal 11 mm) with hista-

From the Division of Clinical Immunology, Mount Sinai Medical Center, New York, New York

Supported by National Institutes of Health Grant CA-R-29-256990 and the Irma T. Hirschl Career trust

Address correspondence and reprint requests to Dr. Kirk Sperber, Division of Clinical Immunology, Mount Sinai Medical Center, Box 1089, 1 Gustave Levy Place, New York, NY 10029

mine (1 mg/mL) (Center Laboratories, Port Washington, NY) and diluent controls. To determine that the 5-FU was not a skin irritant, puncture skin testing was also performed on three normal controls with the same concentrations of the drug used to test the patient and was negative. Since the patient required 5-FU in the treatment of her malignancy and had positive skin tests to the drug, she was desensitized using a modified continuous intravenous protocol. 5-FU was serially diluted to a concentration of 0.00010 mg/mL and infused slowly at a rate of 1 mL/minute for 20 minutes using a Flogard volume infusion pump (Baxter, McGraw, IL). The infusion rate was then increased to 3 mL/minute for 20 minutes. Using a 10-fold higher concentration of the drug (0.0010 mg/mL), we followed the same infusion protocol starting at a rate of 1 mL/minute for 20 minutes and then increased it to 3 mL/minute. This cycle was repeated 6 times until we administered the total dosage (~900 mg) required for the chemotherapy (Table I). The infusion lasted 220 minutes and we did not pretreat the patient with antihistamines or steroids. She tolerated the desensitization with no adverse effects. After the desensitization there was no reactivity to 5-FU on repeat puncture skin testing at any concentration of the drug tested. She successfully completed the course of chemotherapy for 20 cycles over the following year, repeating the desensitization protocol for 5-FU before each cycle. She remains tumor free at the present time.

TABLE I

5-Fluorouracil Desensitization Protocol

5-Fluorouracil (5-FU) was First Diluted to a Concentration of 0.00010 mg/mL and Then Infused at a Rate of 1.0 mL/minute for 20 Minutes.

Time (Min)	5-FU Concentration (mg/mL)	Infusion Rate (mL/min)	Cumulative Dose (mg)
0	0.00010	1.0	0
20	0.00010	3.0	0.0020
40	0.0010	1.0	0.0080
60	0.0010	3.0	0.0280
80	0.010	1.0	0.0880
100	0.010	3.0	0.2880
120	0.10	1.0	0.880
140	0.10	3.0	2.880
160	1.0	1.0	8.80
180	1.0	3.0	28.80
200	10.0	1.0	88.80
220	10.0	3.0	288.80
			888.0

The infusion rate was then increased to 3 mL/minute at the same 5-FU concentration for another 20 minutes. This cycle was repeated six times using 10-fold higher concentrations of 5-FU until a cumulative dose of ~900 mg of 5-FU was administered.

DISCUSSION

There are limited reports of systemic anaphylactic reactions to 5-FU. In one case report, a patient with carcinoid syndrome had prolonged hypotension after intravenous 5-FU infusion, which could have been a manifestation of the carcinoid.⁴ In the second case report, a patient with adenocarcinoma of the colon who had received 9 doses of 5-FU (900 mg) had an anaphylactic reaction.⁵ The third patient had an immediate reaction to 5-FU after the first administration that responded to prednisolone therapy.⁶ Intradermal skin testing was positive in this patient, although there were no positive or negative controls and no testing of non-5-FU allergic controls to assess specificity of the 5-FU skin test. Our patient also had an immediate reaction and a positive skin test to 5-FU despite the fact that she had not been previously exposed to the drug. Skin testing for 5-FU is clearly not standardized, and we did not perform in vitro studies to detect specific anti-5-FU IgE antibodies. However, the normal controls did not react to the 5-FU skin test reagents, making it less likely that the positive skin testing was nonspecific. In further support of the validity of the skin testing, the postdesensitization skin testing was negative.

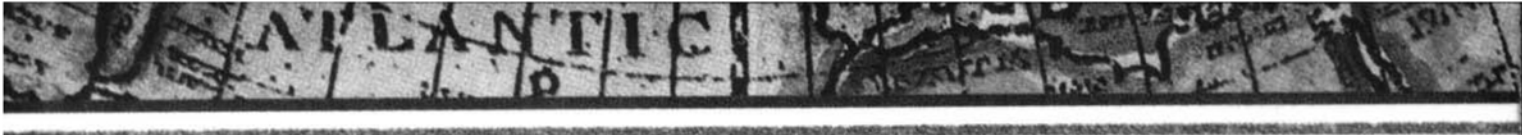
Another possibility to explain the reaction in our patient is that either histamine or some other mediator could have been released by a non-IgE mediated mechanism from either the tumor cells or mast cells after the 5-FU infusion. This may be less likely because the patient had adenocarcinoma of the ovary, which is not generally associated with the production of vasoactive substances. Furthermore, 5-FU has not been reported to release histamine after acute intravenous administration, unlike other chemotherapeutic agents.⁷ She was also pretreated before the second infusion of 5-FU with the radiocontrast treatment protocol, but she still had a systemic reaction.⁸

We desensitized her to 5-FU using a modified intravenous protocol, which has been used for vancomycin desensitization by Wong et al⁹ and Lerner and Dwyer.¹⁰ One adverse reaction to vancomycin, the red man syndrome, is caused by histamine release induced by non-IgE mediated mechanisms and is related to infusion rate.¹¹ Although the 5-FU skin testing was highly suggestive of an IgE mediated reaction, we still could not exclude the possibility of mediator release related to the infusion rate of the drug. In contrast to a conventional desensitization protocol which requires boluses of drug delivered over 3 to 5 minutes followed by an interval of 15 minutes during which there is no drug administered, the continuous infusion protocol delivers small quantities of 5-FU during the entire desensitization. Furthermore, the infusion can be stopped immediately. Because of these advantages, we could more safely and rapidly desensitize our patient to 5-FU than if we used a conventional protocol. This approach may also be useful to desensitize to other drugs where there are no standardized skin tests.

In conclusion, patients who have had systemic reactions to 5-FU may be successfully desensitized using a continuous infusion protocol by sequential increments in the administration of the drug.

REFERENCES

1. Chabner BA, Collins JM (eds). *Cancer Chemotherapy: Principles and Practice*. Philadelphia: JB Lippincott, 1991.
2. Cohen SS, Flaks JG, Barner HD, et al. The mode of action of 5-fluorouracil and its derivatives. *Proc Natl Acad Sci USA* 44:1004–1012, 1958.
3. Calabresi P, Schein PS, Rosenberg SA. *Medical Oncology: Basic Principles and Clinical Management of Cancer*. New York: Macmillan, 1985.
4. DeBeer R, Kabakow B. Anaphylactoid reaction associated with intravenous administration of 5-fluorouracil. *N Y State J Med* 79: 1750–1751, 1979.
5. Batemen JR, Pugh RP, Cassidy FR, et al. 5-Fluorouracil given once weekly: Comparison of intravenous and oral administration. *Cancer* 28:907–917, 1971.
6. Santos AM, Sanchiz-Medina F. Anaphylactic reaction following IV administration of 5-fluorouracil. Letter to the Editor. *Cancer Treat Rep* 70:1346, 1986.
7. Eschaliere A, Lavarenne J, Burtin C, et al. Study of histamine release induced by acute administration of anti-tumor agents in dogs. *Cancer Chemother Pharmacol* 21:246–250, 1998.
8. Greenberger P, Patterson R, Kelly J, et al. Administration of radiocontrast media in high risk patients. *Invest Radiol* 15:S40–43, 1980.
9. Wong J, Ripple R, MacLean JA, et al. Vancomycin hypersensitivity: synergism with narcotics and “desensitization” by a rapid continuous intravenous protocol. *J Allergy Clin Immunol* 94:189–194, 1994.
10. Lerner A, Dwyer JM. Desensitization to vancomycin. *Ann Int Med* 100:157, 1984.
11. Wallace MR, Mascola JR, Oldfield EC. Red man syndrome: Incidence, etiology, and prophylaxis. *J Infect Dis* 164:1180–1185, 1991. □



CURRENT BOOK

COLUMBUS AND THE NEW WORLD : MEDICAL IMPLICATIONS

Edited by GUY A. SETTIPANE, M.D.

Clinical Professor of Medicine
Brown University, Providence, RI

"...I have been using as a textbook The Columbian Exchange by Crosby, for the last four years. However, I have been looking for a book with information that students could apply better. I think this book provides the (reader) not only with the historical context but also with the legacy of the exchange in our present times...We will adapt this excellent book as one of the textbooks for the course, Columbus and His Time."

History and Honors Program, Atlantic Union College

"...One need not be a professional historian or medical specialist to find enjoyment in its provocative detail, tantalizing illustrations and illuminating discussions of unusual topics."

Providence Journal, October 19, 1995

This new international book is unique in that modern medical knowledge was used to answer the many puzzling questions about diseases that devastated the Native American Indians (Amerindians). For example, why were the Amerindians so susceptible to European childhood diseases? Why were these diseases so severe as to cause millions of Amerindians to die? What were these diseases? How were they transmitted to the Native American Indians? What diseases did the Indians introduce to the Europeans? What role did swine influenza play?

The new techniques of HLA tissue typing have enabled us to analyze the genetics of present day Amerindians. Did the incorporation of new genetic material from the old world enable the Native Indians to fight infections better? What percentage of the present day Indian population have European, Oriental, and African HLA blood and tissue types?

In this book we have gathered some of the world's great medical specialists to help answer these questions. These specialists include health scientists from Mexico, Ecuador, France, Belgium, Canada and the U.S.A. Three of the United States authors are from the National Institute of Health at Bethesda, Maryland. One author is the Minister of Public Health of Ecuador (Plutarco Naranjo, M.D.). The opinions and conclusions from these experts are based on the best scientific knowledge available today.

To order: remit check or money order, \$49.50 (Hardcover)

MLA797

OceanSide Publications Inc.

95 Pitman Street

Providence, Rhode Island 02906 U.S.A.

Visa/MasterCard accepted

Outside U.S.A. please add \$30.00

148 pages

36 Illustrations

ISBN 0-936587-07-5

Phone (401) 331-2510

FAX (401) 331-5138

**an effective
asthma controller therapy
that's one tablet daily
and not a steroid?**



**it's a
reality.**

**Start with SINGULAIR for the prophylaxis and chronic treatment
of asthma in patients 6 years of age and older**

- SINGULAIR should not be used as rescue medication to treat acute asthma episodes. Patients should be advised to have appropriate rescue medication available.
- Use of SINGULAIR may not eliminate the need for inhaled or systemic corticosteroids. Patients should not decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- SINGULAIR is contraindicated in patients with hypersensitivity to any component of this product.

Please read the Brief Summary of Prescribing Information on the reverse side.

For more information visit us at <http://www.singulair.com>

SINGULAIR is a registered trademark of Merck & Co., Inc.

991225(3)(802)-SNG © 1999 Merck & Co., Inc. All rights reserved.



ONCE DAILY
SINGULAIR[®]
(MONTELUKAST SODIUM)

E f f e c t i v e l y h e l p s c o n t r o l a s t h m a

Brief Summary

SINGULAIR® (montelukast sodium) tablets

INDICATIONS AND USAGE

SINGULAIR is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 6 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

General

SINGULAIR is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have appropriate rescue medication available. Therapy with SINGULAIR can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR should not be abruptly substituted for inhaled or oral corticosteroids.

SINGULAIR should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled β -agonists as prophylaxis and have available for rescue a short-acting inhaled β -agonist.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. Although SINGULAIR is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients (see CLINICAL PHARMACOLOGY, Clinical Studies, in the full Prescribing Information).

Eosinophilic Conditions

In rare cases, patients on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients

- Patients should be advised to take SINGULAIR daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral tablets of SINGULAIR are not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β -agonist medication available to treat asthma exacerbations.
- Patients should be advised that, while using SINGULAIR, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for 24-hour period are needed.
- Patients receiving SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled β -agonists as prophylaxis unless otherwise instructed by their physician. All patients should have available for rescue a short-acting inhaled β -agonist.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.

Chewable Tablets

- Phenylketonurics:** Phenylketonuric patients should be informed that the chewable tablet contains phenylalanine (a component of aspartame) 0.842 mg per 5-mg chewable tablet.

Drug Interactions

SINGULAIR has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin.

Although additional specific interaction studies were not performed, SINGULAIR was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in a 2-year carcinogenicity study in Sprague-Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (approximately 160 times the maximum recommended daily oral dose in adults and 190 times the maximum recommended daily oral dose in children, on a mg/m² basis) or in a 92-week carcinogenicity study in mice at oral doses up to 100 mg/kg/day (approximately 40 times the maximum recommended daily oral dose in adults and 50 times the maximum recommended daily oral dose in children, on a mg/m² basis).

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (approximately 160 times the maximum recommended daily oral dose in adults, on a mg/m² basis). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (approximately 80 times the maximum recommended daily oral dose in adults, on a mg/m² basis). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (approximately 650 times the maximum recommended daily oral dose in adults, on a mg/m² basis).

Pregnancy, Teratogenic Effects

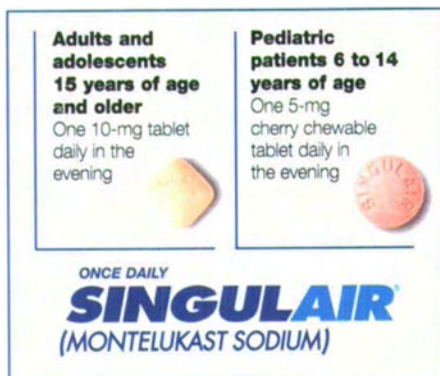
Pregnancy Category B:

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (approximately 320 times the maximum recommended daily oral dose in adults, on a mg/m² basis) and in rabbits at oral doses up to 300 mg/kg/day (approximately 490 times the maximum recommended daily oral dose in adults, on a mg/m² basis). Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to SINGULAIR while pregnant. Healthcare providers are encouraged to report any prenatal exposure to SINGULAIR by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in



human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR® (montelukast sodium) is given to a nursing mother.

Pediatric Use

The safety and effectiveness in pediatric patients below the age of 6 years have not been established. Long-term trials evaluating the effect of chronic administration of SINGULAIR on linear growth in pediatric patients have not been conducted.

Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adolescents and Adults 15 Years of Age and Older

SINGULAIR has been evaluated for safety in approximately 2600 adolescent and adult patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAIR occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo, regardless of causality assessment:

Adverse Experiences Occurring in $\geq 1\%$ of Patients
with an Incidence Greater than that in Patients Treated with Placebo,
Regardless of Causality Assessment

	SINGULAIR 10 mg/day (%) (n=1955)	Placebo (%) (n=1180)
Body As A Whole		
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous System/Psychiatric		
Dizziness	1.9	1.4
Headache	18.4	18.1
Respiratory System Disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/Skin Appendages Disorder		
Rash	1.6	1.2
Laboratory Adverse Experiences*		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

*Number of patients tested (SINGULAIR and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

The frequency of less common adverse events was comparable between SINGULAIR and placebo.

Cumulatively, 569 patients were treated with SINGULAIR for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age

SINGULAIR has also been evaluated for safety in approximately 320 pediatric patients 6 to 14 years of age. Cumulatively, 169 pediatric patients were treated with SINGULAIR for at least 6 months, and 121 for one year or longer in clinical trials. The safety profile of SINGULAIR versus placebo in the double-blind, 8-week, pediatric efficacy trial was generally similar to the adult safety profile with the exception of the adverse events listed below. In pediatric patients receiving SINGULAIR, the following events occurred with a frequency $\geq 2\%$ and more frequently than in pediatric patients who received placebo, regardless of causality assessment: diarrhea, laryngitis, pharyngitis, nausea, otitis, sinusitis, and viral infection. The frequency of less common adverse events was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use: hypersensitivity reactions, including anaphylaxis, angioedema, pruritus, and urticaria.

In rare cases, patients on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see PRECAUTIONS, Eosinophilic Conditions).

OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (approximately 2000 times the maximum recommended daily oral dose in adults and 2400 times the maximum recommended daily oral dose in children, on a mg/m² basis) and rats (approximately 4100 times the maximum recommended daily oral dose in adults and 4800 times the maximum recommended daily oral dose in children, on a mg/m² basis).

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.



For more detailed information, consult your Merck Representative or read the complete Prescribing Information.

© 1999 Merck & Co., Inc., West Point, PA 19486.

991225(3)(802)-SNG

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.