

Hydrocortisone sodium succinate does not cross-react with aspirin in aspirin-sensitive patients with asthma

Bernard A. Feigenbaum, MD, Donald D. Stevenson, MD, and
Ronald A. Simon, MD La Jolla, Calif.

Background: Bronchospasm after intravenous hydrocortisone treatment has been reported in some patients with aspirin-sensitive respiratory disease.

Objective: This study was designed to determine the prevalence of sensitivity to hydrocortisone among patients with aspirin-sensitive respiratory disease.

Methods: We performed double-blind, placebo-controlled challenges with aspirin and 100 mg of hydrocortisone sodium succinate administered intravenously in 53 subjects.

Results: Forty-five of the 53 subjects (85%) undergoing oral aspirin challenge experienced respiratory reactions to aspirin. Forty-four of these 45 patients had neither naso-ocular, cutaneous, nor respiratory reactions to hydrocortisone sodium succinate. One aspirin-sensitive subject had bronchospasm and a naso-ocular reaction to hydrocortisone sodium succinate and a naso-ocular reaction with minimal bronchospasm to methylprednisolone sodium succinate. After desensitization to aspirin, and while receiving maintenance aspirin therapy, this subject again reacted to hydrocortisone sodium succinate with bronchospasm and naso-ocular reaction.

Conclusion: We conclude that aspirin-sensitive patients with asthma are not preferentially sensitive to hydrocortisone and that hydrocortisone sodium succinate does not cross-react or cross-desensitize with aspirin. (*J ALLERGY CLIN IMMUNOL* 1995;96:545-8.)

Key words: Adverse reaction, asthma, aspirin, aspirin-sensitive asthma, aspirin-sensitive respiratory disease, bronchospasm, corticosteroids, hydrocortisone, methylprednisolone, succinate

Corticosteroids are routinely used in the treatment of asthma. Since the report of an anaphylactic reaction to hydrocortisone sodium succinate administered intravenously (hydrocortisone-ss) in 1974¹ and after several anecdotal reports of similar reactions in patients with aspirin-sensitive respiratory disease,² there have been concerns about the frequency of these reactions. In 1981, Dajani et al.³ reported bronchospastic reactions to hydrocortisone-ss in three of 11 aspirin-sensitive patients with asthma. In 1985, Szczeklik et al.⁴ found a 10% incidence of airflow obstruction in 31 aspirin-

Abbreviations used

FEV ₁ :	Forced expiratory volume in 1 second
Hydrocortisone-ss:	Hydrocortisone sodium succinate administered intravenously
Methylprednisolone-ss:	Methylprednisolone sodium succinate administered intravenously
NSAID:	Nonsteroidal antiinflammatory drug

From the Scripps Clinic and Research Foundation and the Scripps Research Institute, La Jolla, Calif.

Supported by National Institutes of Health grants M01RR00833 and AI-32834.

Received for publication Sept. 15, 1994; revised Feb. 9, 1995; accepted for publication Feb. 10, 1995.

Reprint requests: Donald D. Stevenson, MD, Allergy-W205, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, CA 92037.

Copyright © 1995 by Mosby-Year Book, Inc.
0091-6749/95 \$5.00 + 0 1/1/64143

sensitive patients with asthma undergoing challenge with hydrocortisone-ss.

Individuals with aspirin-sensitive respiratory disease have underlying chronic rhinitis, sinusitis, nasal polyps, and asthma and experience acute inflammation of the respiratory tract after ingestion of aspirin.⁵ The hallmark of aspirin sensitivity is the appearance of naso-ocular congestion and

rhinorrhea and an acute, severe, asthma attack within 20 minutes to 3 hours after ingesting an ordinary dose of aspirin or nonsteroidal antiinflammatory drug (NSAID). All aspirin-sensitive patients with asthma are capable of being desensitized to aspirin and remain tolerant to aspirin and cross-reacting substances, such as NSAIDs, as long as they ingest at least 325 mg of aspirin a day.⁵

This study was designed to determine the prevalence of sensitivity to hydrocortisone-ss among subjects with aspirin-sensitive respiratory disease. In addition, we proposed to determine whether hydrocortisone-ss cross-reacts with aspirin and whether hydrocortisone-ss-sensitive subjects who are desensitized to aspirin become desensitized to hydrocortisone-ss, the expected event for true cross-reacting chemicals.

METHODS

Fifty-three patients with well-controlled asthma who gave a history of an asthmatic reaction to aspirin or NSAIDs were referred to our center and enrolled in the study. No subject had a known prior reaction to corticosteroids. Approval was obtained from the Human Subjects Committee, and all subjects were admitted to the General Clinical Research Center and gave informed consent.

Usual medications such as inhaled and systemic corticosteroids, theophylline, and oral bronchodilators were continued through the challenges. Cromolyn sodium and antihistamines were discontinued for at least 24 hours, and inhaled bronchodilators were discontinued for at least 12 hours before challenges.

Forced expiratory volume in 1 second (FEV₁) and forced vital capacity were recorded during the challenge periods at 1-hour intervals or when symptoms developed. On day 1, single-blind challenges with placebo were conducted at 3-hour intervals to establish airway stability. Subjects with unstable airways (variation in FEV₁ of >15% during the 9-hour study) were treated until stable or else discharged and rescheduled for admission at a later date.⁶ On day 2, subjects underwent a double-blind, placebo-controlled challenge with acetaminophen as part of another study.

On day 3 of challenges, patients received three double-blind, placebo-controlled intravenous challenges. One of three solutions contained 100 mg of hydrocortisone-ss. The other two solutions contained saline. The solutions were mixed by one nurse and given "blinded" to another nurse, who then administered the solutions at 1-hour intervals.

Patients were observed for naso-ocular, cutaneous, or respiratory signs and symptoms; and FEV₁ was measured every half hour. A decrease in FEV₁ of 20% or more, with or without associated naso-ocular reaction, within 1 hour of challenge with hydrocortisone-ss was considered a significant bronchospastic response. A 15%

to 20% decrease of FEV₁ was considered significant if associated with a simultaneous naso-ocular or cutaneous reaction.

On day 4, any patient who reacted to hydrocortisone-ss was challenged with 40 mg of methylprednisolone sodium succinate administered intravenously (methylprednisolone-ss). All subjects then underwent oral aspirin challenges with doses increasing from 30 to 650 mg according to a previously described standardized protocol.⁶ A decrease in FEV₁ of 20% or more, with or without associated naso-ocular reaction, within 3 hours of challenge with aspirin was considered a significant bronchospastic response. A 15% to 20% decrease of FEV₁ was considered significant if associated with a simultaneous naso-ocular or cutaneous reaction. All subjects who had reactions to aspirin were eventually desensitized to 650 mg of aspirin.

RESULTS

Forty-five of the 53 subjects (85%) undergoing oral aspirin challenge experienced respiratory reactions to aspirin. Forty-four of these 45 patients had neither naso-ocular, cutaneous, nor respiratory reactions to hydrocortisone-ss.

The only reactor to hydrocortisone-ss was a 40-year-old woman. Twenty minutes after hydrocortisone-ss challenge, the subject experienced sneezing, ocular injection, and an 18% decrease in FEV₁. Challenge the next day (day 4), with 40 mg of methylprednisolone-ss, caused a 10% decrease in FEV₁ and a naso-ocular reaction 35 minutes after challenge.

On day 5, FEV₁ decreased 51%, and naso-ocular congestion developed 1 hour after the subject received 100 mg aspirin. The subject was ultimately desensitized to 650 mg of aspirin on day 7. Open challenge was repeated on day 8 with 100 mg of hydrocortisone-ss and caused a 39% decrease in FEV₁ with ocular injection and periorbital edema with onset 15 minutes after injection of hydrocortisone-ss (Table I).

DISCUSSION

The question of whether patients with aspirin-sensitive respiratory disease are likely to have respiratory reactions to intravenous corticosteroid preparations is both academic and practical. These medications are potent antiinflammatory agents and are frequently given to patients with asthma attacks. The choice of corticosteroid might be influenced by a high incidence of reactions to certain preparations.

We find a very low incidence (2%) of sensitivity to hydrocortisone-ss among patients with aspirin-sensitive respiratory disease, suggesting that there

TABLE I. Results of challenges: Days 1 through 8 in patient reacting to hydrocortisone-ss

Day	Substance	Dose (mg)	Reaction time (min)	FEV ₁	Reaction
1	Placebo × 3				None
2	Acetaminophen	1000, 1500			None
3	Sulfites	5 to 200			None
3	IV placebo × 2				None
3	Hydrocortisone-ss	100	20	2.77 (↓ 18%)	Wheezing, sneezing, naso-ocular
4	IV placebo				None
4	Methylprednisolone-ss	40	35	2.92 (↓ 10%)	Headache, dizziness, ocular
4	Aspirin	30, 60			None
5	Aspirin	100	60	1.50 (↓ 51%)	Wheezing, sneezing, naso-ocular
6	Aspirin	100 to 325			None
7	Aspirin	650	135	2.99 (↓ 11%)	Sneezing, naso-ocular
7	Aspirin	650			None
8	Hydrocortisone-ss	100	15	2.26 (↓ 39%)	Wheezing, sneezing, naso-ocular

IV, Intravenous.

is no obvious connection between the two sensitivity states. Anaphylactoid reactions to hydrocortisone-ss are not limited to patients with aspirin-sensitive respiratory disease.^{7,8} Patients with aspirin-sensitive respiratory disease tend to have severe asthma and are likely to be hospitalized and treated with intravenous corticosteroid preparations. Repeated exposure to intravenous corticosteroids would increase the opportunity of sensitization to these drug antigens.

The only subject who reacted to hydrocortisone-ss also possibly reacted to methylprednisolone-ss, although not to the threshold of a 15% decrease in FEV₁. There are several explanations for the lesser reaction to methylprednisolone-ss. First, there is approximately 60% less succinate ester in 40 mg of methylprednisolone-ss compared with 100 mg of hydrocortisone-ss. Second, partial desensitization may have occurred because the methylprednisolone-ss challenge was administered less than 20 hours after the hydrocortisone-ss reaction.

It seems likely that a chemical structure that is common to preparations of both hydrocortisone-ss and methylprednisolone-ss induced the reactions. Dajani et al.³ and later Szczeklik et al.⁴ showed that the intravenous solvent was not the cause of the reactions to hydrocortisone, which they reported. There are several reported cases^{9,10,11} of positive skin test responses to hydrocortisone-ss and methylprednisolone-ss in patients who had anaphylactic reactions to these compounds. Native molecules of succinate and hydrocortisone would not be expected to cause IgE formation. Theoretically, the combination of hydrocortisone and succinate, as hydrocorti-

sone-ss, may stimulate formation of specific IgE.⁸ This hypothesis was not tested in our patient because she became unavailable for skin testing.

The properties of methylprednisolone-ss *in vivo* are well characterized. The serum half-life was 4.14 ± 1.62 minutes for intravenous doses of 80 mg or less in one study¹² and 15 minutes for an 80 mg intravenous dose in another study.¹³ Up to 10% of the dose is excreted unchanged in the urine. Assuming 5 half-lives for near total clearance, whole methylprednisolone-ss molecules would have 20 to 75 minutes to induce an IgE response, even without tissue binding.

Desensitization to aspirin did not prevent naso-ocular or bronchospastic reactions to hydrocortisone-ss in this subject. Such a finding strongly supports the hypothesis that hydrocortisone-ss sensitivity is unrelated to aspirin sensitivity because all other drugs that cross-react with aspirin also cross-desensitize with aspirin.^{14,15,16}

We conclude that aspirin-sensitive patients with asthma are not preferentially sensitive to hydrocortisone-ss. Hydrocortisone-ss does not cross-react with aspirin because aspirin desensitization did not prevent the second reaction to hydrocortisone-ss. The reactions in this subject to two different succinate preparations suggest the possibility of an IgE-mediated reaction to succinate esters. We do not recommend withholding intravenous hydrocortisone, including hydrocortisone-ss, from aspirin-sensitive patients with asthma.

We thank Drs. James Baldwin, Sanara Christiansen, Pamela Daffern, David Mathison, and Bruce Zuraw; Marcia Hankammer, RN; and the other General Clinic

Research Center nurses and administrators for their invaluable help.

REFERENCES

1. Mendelson LM, Meltzer ED, Hamburger RN. Anaphylaxis-like reactions to corticosteroid therapy. *J ALLERGY CLIN IMMUNOL* 1974;54:125-31.
2. Partridge MR, Gibson GJ. Adverse bronchial reactions to intravenous hydrocortisone in two aspirin-sensitive asthmatic patients. *Br Med J* 1978;1:1521-2.
3. Dajani BM, Sliman NA, Shubair KS, Hamzeh YS. Bronchospasm caused by intravenous hydrocortisone sodium succinate (Solu-cortef) in aspirin-sensitive asthmatics. *J ALLERGY CLIN IMMUNOL* 1981;68:201-4.
4. Szczeklik A, Nizankowska E, Czerniawska-Mysik G, Sek S. Hydrocortisone and airflow impairment in aspirin-induced asthma. *J ALLERGY CLIN IMMUNOL* 1985;76:530-6.
5. Manning ME, Stevenson DD, Mathison DA. Reactions to aspirin and other nonsteroidal anti-inflammatory drugs. *Immunol Allergy Clin North Am* 1992;12:611-31.
6. Stevenson DD. Oral challenges to detect aspirin and sulfite sensitivity in asthma. *N Engl Regional Allergy Proc* 1988;9:135-42.
7. Fulcher DA, Katelaris CH. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review. *Med J Aust* 1991;154:210-4.
8. Mansfield LE, Ting S, Haverly RW. Anaphylaxis caused by the sodium succinate ester of hydrocortisone and methylprednisolone. *J Asthma* 1986;23:81-3.
9. Freedman MD, Schocket AL, Chapel N, Gerber J. Anaphylaxis after intravenous methylprednisolone administration. *JAMA* 1981;245:607-8.
10. Rodger RS. Anaphylaxis following treatment with a corticosteroid report of one case. *Clin Allergy* 1983;13:499-500.
11. Goldstein DA, Zimmerman B, Spielberg SP. Anaphylactic response to hydrocortisone in childhood: a case report. *Ann Allergy* 1985;55:599-600.
12. Al-Habet SM, Rogers HJ. Methylprednisolone pharmacokinetics after intravenous and oral administration. *Br J Clin Pharmacol* 1989;27:285-90.
13. Derendorf H, Mollmann H, Rohdewald P, et al. Kinetics of methylprednisolone and its hemisuccinate ester. *Clin Pharmacol Ther* 1985;37:502-7.
14. Pleskow WW, Stevenson DD, Mathison DA, Simon RA. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J ALLERGY CLIN IMMUNOL* 1982;69:11-9.
15. Settiple RA, Stevenson DD. Cross sensitivity with acetaminophen in aspirin-sensitive subjects with asthma. *J ALLERGY CLIN IMMUNOL* 1989;84:26-33.
16. Stevenson DD, Hougham AJ, Schrank PJ, et al. Salsalate cross-sensitivity in aspirin-sensitive patients with asthma. *J ALLERGY CLIN IMMUNOL* 1990;86:749-58.