



BY WILLIAM G. WILKOFF, M.D.

## LETTERS FROM MAINE

# “We the [Imperfect] People ...”

A few months ago, I was invited to a retirement party for an old house-officer mate. He wasn't actually retiring, but he was calling it quits from active clinical practice. The food was good

and the wine was very good, but the rest of the event left me feeling a bit sour.

The roasts and toasts began with the usual (and well-deserved) compliments by his coworkers. But one of the contributors spoke about how envious she was of my friend because she herself was eagerly anticipating a time when she would no longer have to deal with the stupid and inconsiderate (my words, not hers) patients and parents. She intended her observa-

tions to be humorous. However, her scenarios triggered a half-hour-long anecdote-sharing competition during which each physician who stood up tried to one-up his colleagues with a tale of how dumb patients can be. Or, how badly he had been abused by a thoughtless parent who called at an inconvenient time with what he felt was a trivial question.

I must admit that some of the stories made me chuckle until I stepped back and

took a longer look at the tableau spread out before me. It bothered me for two reasons. First, we may not like to admit it, but almost every joke is “on” someone. And here I was listening to a bunch of physicians who in the frivolity of the moment were willing to make the patients they served into the butt of their humor.

Physicians must continually struggle with the “we-they” divide. On one hand, it can be important to maintain a reputation and demeanor that give our advice credibility. A patient or a parent facing the unknown of a serious disease is often looking for someone with more “authority” whom can be trusted. On the other hand, we must remember that “the sore throat in Room 7” belongs to another human being who, when all is said and done, is no different from us.

Almost every survey about medical care that I have seen in the last few years contains responses that make it clear that consumers, patients, clients—whoever—want good customer service. Nearly every week I find myself having to remind a receptionist or assistant to reconsider a response to a parent. “What would you have said if your daughter had been the patient?” I think it was Pogo the comic-strip possum who said, “We have met the enemy and he is us.” Customer service boils down to accepting the reality that we are all in this together and so we might as well treat each other as equals.

The second troubling concern that surfaced as I waited for the anecdote swapping to end was that this event had seemed to unroof a festering sore of dissatisfied physicians. Maybe I am reading more into this alcohol-enabled complaint session than I should. But, I have read somewhere that when older physicians are asked if they would encourage young people to enter medicine, many of them reply that they wouldn't.

What is it about being a physician in the new millennium that is making us such an unhappy bunch? Certainly, hassles with third-party payers and the ever-present threat of a malpractice suit can put a few dark clouds in your sky. But listening to these doctors, it sounds as though the day-in and day-out interaction with patients, or certainly with parents, might be a significant source of discontent among some of them.

I've always figured that medicine—and definitely pediatrics—is a people business. And we the people are a quirky sort. We do dumb things with great frequency, and from time to time even the most saintly among us behave inconsiderately. Failure to accept those basic facts of life might be at the root of some of our discontent.

And there might be a good argument for requiring all medical students to have a real job, such as waiting tables, before they start their formal medical education. It might just cut down on the whining. ■

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**Table 1:** Adverse Reactions with  $\geq 3\%$  Incidence Reported in Patients  $\geq 12$  Years of Age with ALVESCO in US Placebo-Controlled Clinical Trials in Patients Previously on Bronchodilators and/or Inhaled Corticosteroids

Adverse Reaction	Placebo (N=507) %	ALVESCO		
		80 mcg BID (N=325) %	160 mcg BID (N=127) %	320 mcg BID (N=172) %
Headache	7.3	4.9	11.0	8.7
Nasopharyngitis	7.5	10.5	8.7	7.0
Sinusitis	3.0	3.1	5.5	5.2
Pharyngolaryngeal pain	4.3	4.3	2.4	4.7
Upper respiratory Inf.	6.5	7.1	8.7	4.1
Arthralgia	1.0	0.9	2.4	3.5
Nasal congestion	1.6	1.8	5.5	2.9
Pain in extremity	1.0	0.3	3.1	2.3
Back pain	2.0	0.6	3.1	1.2

The following adverse reactions occurred in these clinical trials using ALVESCO with an incidence of less than 1% and occurred at a greater incidence with ALVESCO than with placebo.

**Infections and Infestations:** Oral candidiasis

**Respiratory Disorders:** Cough

**Gastrointestinal Disorders:** Dry mouth, nausea

**General disorders and administrative site conditions:** Chest discomfort

**Respiratory, Thoracic, and Mediastinal Disorders:** Dysphonia, dry throat

The fifth study was a 12-week clinical trial in asthma patients 12 years of age and older who previously required oral corticosteroids (average daily dose of oral prednisone of 12 mg/day), in which the effects of ALVESCO 320 mcg twice daily (n = 47) and 640 mcg twice daily (n = 49) were compared with placebo (n=45) for the frequency of reported adverse reactions. The following adverse reactions occurred at an incidence of  $\geq 3\%$  in the ALVESCO-treated patients and were more frequent compared to placebo: sinusitis, hoarseness, oral candidiasis, influenza, pneumonia, nasopharyngitis, arthralgia, back pain, musculoskeletal chest pain, headache, urticaria, dizziness, gastroenteritis, face edema, fatigue, and conjunctivitis.

**Pediatric Patients 4 to 11 Years of Age**

The safety of ALVESCO in pediatric patients 4 to 11 years of age was evaluated in two studies in which ALVESCO 40 mcg, 80 mcg, and 160 mcg was administered once daily for 12 weeks.

**Pediatric Patients under 4 Years of Age**

Studies have not been conducted in patients under 4 years of age.

**Long-Term Clinical Trials Experience**

A total of 197 patients 12 years of age and older (82 males and 115 females) from one of the 12-week treatment placebo-controlled studies were re-randomized to ciclesonide 320 mcg twice daily and followed for one year. The safety profile from the one-year follow up was similar to that seen in the 12- and 16-week treatment studies. Long term safety information for pediatric patients 4 to 11 years of age is obtained from three open label one year safety studies.

**Post-marketing Experience**

In addition to adverse reactions identified from clinical trials, the following adverse reactions have been identified during worldwide post-marketing use of ciclesonide oral inhalation. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Immediate or delayed hypersensitivity reactions such as angioedema with swelling of the lips, tongue and pharynx.

**DRUG INTERACTIONS**

In clinical studies, concurrent administration of ciclesonide and other drugs commonly used in the treatment of asthma (albuterol, formoterol) had no effect on pharmacokinetics of des-ciclesonide.

*In vitro* studies and clinical pharmacology studies suggested that des-ciclesonide has no potential for metabolic drug interactions or protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects:** Pregnancy Category C

Oral administration of ciclesonide in rats up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg/day (less than the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily inhalation dose based on mcg/m<sup>2</sup>).

There are no adequate and well-controlled studies in pregnant women. ALVESCO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

**Non-teratogenic Effects:**

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

**Nursing Mothers**

It is not known if ciclesonide is secreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal, but detectable levels of ciclesonide were recovered in milk. Caution should be used when ALVESCO is administered to nursing women.

**Pediatric Use**

The safety and effectiveness of ALVESCO in children under 12 years of age have not been established.

Two randomized double-blind placebo-controlled studies were conducted to evaluate the efficacy of ALVESCO 40, 80, or 160 mcg administered once daily for 12 weeks in patients 4 to 11 years of age with asthma. These studies included 1018 patients previously using either controller therapy (predominately inhaled corticosteroids) or reliever therapy (bronchodilator therapy alone). The patients had a mean baseline percent predicted FEV<sub>1</sub> of 68%. The primary efficacy endpoint was morning pre-dose FEV<sub>1</sub>. Other measures of efficacy included AM PEF, asthma symptoms, and rescue albuterol use. The studies showed inconsistent results and do not establish the efficacy of ALVESCO in patients 4 to 11 years of age.

The safety of ALVESCO was evaluated in 957 children between the ages of 4 and 11 who were treated with ALVESCO in the two controlled clinical studies, 2 open label one-year safety extensions of the controlled clinical studies, and one open label safety study. In the controlled studies, the distribution of adverse events in the ALVESCO and placebo groups was similar. The type of adverse events reported were similar to events reported in this patient population with other inhaled corticosteroids. The open label safety studies compared the safety of ALVESCO in doses up to 160 mcg once daily with an orally inhaled corticosteroid comparator. The types of adverse events seen were similar to those seen in the 12-week controlled studies.

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height are unknown. The potential for “catch up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving orally inhaled corticosteroids including ALVESCO should be monitored routinely (e.g., via stadiometry).

A 52-week, multi-center, double-blind, randomized, placebo-controlled parallel-group study was conducted to assess the effect of orally inhaled ciclesonide on growth rate in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the baseline, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this study because compliance could not be assured. There was no difference in efficacy measures between the placebo and the ALVESCO groups. Ciclesonide blood levels were also not measured during the one-year treatment period.

The potential growth effects of prolonged treatment with orally inhaled corticosteroids should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of orally inhaled corticosteroids, including ALVESCO, each patient should be titrated to his/her lowest effective dose.

**Geriatric Use**

Clinical studies of ALVESCO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**OVERDOSAGE**

Chronic overdosage may result in signs/symptoms of hypercorticism. ALVESCO was well tolerated following inhalation by healthy subjects of single doses of 2880 mcg. A single oral dose of up to 10 mg of ciclesonide in healthy subjects was well tolerated and serum cortisol levels were virtually unchanged in comparison with placebo treatment. Adverse reactions were of mild or moderate severity.

The median lethal doses in mice and rats after single oral and intraperitoneal administration were >2000 mg/kg and >200 mg/kg, respectively. These doses are >12000 and >2500 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg/day (approximately 6 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg/day (approximately 2 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) in rats for 104 weeks.

Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings.

No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day).



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