What to Say and Do When Vaccine Refusal Occurs

BY SHERRY BOSCHERT

San Francisco Bureau

SAN FRANCISCO — Communication skills are key when talking to parents who are reluctant to immunize their children, judging by results of one of the first observational studies of these encounters in private practice.

A pilot study recruited seven pediatricians and two family physicians in Louisville, Ky., for a "field test" of using

"standardized patients" in primary care practice settings, Dr. Kristina Bryant said at the annual meeting of the American Academy of Pediatrics. Standardized patients are actors or actresses who are trained to portray patients and are commonly used in medical schools to help teach and test students.

The physicians were told that a standardized patient would visit their office within 6 months, but were not told what the standardized patient would do or say, explained Dr. Bryant of the University of Louisville (Ky.). Dr. Bryant is associated with several companies that make vaccines. She is on the speakers' bureaus of Sanofi Pasteur and Abbott Laboratories. and she has received research funds from Merck & Co., MedImmune, Wyeth Pharmaceuticals, and GlaxoSmithKline.

The actresses in the study pretended to be pregnant women who had just moved to the area and were looking for a pediatrician. They portrayed 24- to 30-yearold married women who were "pregnant" for the first time; they simulated pregnancy with a padded belly kit. "We actually had pediatricians patting the mother's tummy," Dr. Bryant said. "It was

The standardized patients presented themselves as upper middle class, college educated, and Internet savvy women. They paid for the visit out of pocket, claiming that their insurance was pending and they didn't have insurance cards yet.

Each woman told the physicians that she didn't want to immunize her child because she believed the MMR vaccine causes autism and the varicella vaccine causes neurologic damage. In addition, she said that too many vaccines overload the immune system, that the AAP and the Centers for Disease Control and Prevention are not truthful, and that she did not believe her child was at risk for getting measles, diphtheria, or other diseases anyway.

The standardized patients graded physicians on a survey after each encounter, and recordings of four encounters were transcribed and analyzed by the investigators.

Physicians scored very well in listening to the mother's concerns about vaccines, maintaining eye contact, spending adequate time with the mother (a median of 19 minutes per visit), using understandable terms, and behaving in a nonpaternalistic manner, reported Dr. Bryant and her associates. They also scored well in eliciting the mother's agenda for the visit, avoiding interrupting, and being warm, compassionate, and nonjudgmental.

Physicians did not score as well on 'characteristics that are important not just in vaccination risk/benefit communications, but in communications with families in general," she said. These included introducing themselves and welcoming the mother, expressing interest in the mother, asking open-ended questions, and encouraging questions from the mother. Scores also were lower in checking for the mother's understanding, validating the importance of her concerns, assessing the mother's knowledge about vaccines, and summarizing at the end of the visit.

Among the four physicians who were recorded, only three discussed the risks and benefits of vaccines, and only two presented scientific evidence to refute the mother's claims that MMR causes autism or that thimerosal is dangerous.

Two referred mothers to the AAP and CDC Web sites for more information, and two offered to delay some vaccinesa strategy recommended by the AAP when dealing with reluctant parents. None explored cost as a potential barrier to immunization.

Two gave the mothers inaccurate information. One said he would have to contact Child Protective Services if the mother refused to vaccinate her child. The other said that the child could not attend public school unless immunized, but Kentucky allows religious exemptions.

"The plus side is that none of these physicians refused to care for this family if the mother refused immunizations, and [all] talked about [vaccine refusal] being addressed at future visits," Dr. Bryant said. ■

Axid[®] (nizatidine) **Oral Solution**

BRIEF SUMMARY: Please see package insert for full prescribing information.

arragonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarly by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see Dosage and Administration).

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

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Drug Interactions—No interactions have been observed between nizatidine and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin dally, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently. Carcinogenesis, Mutagenesis, Impairment of Fertilitly—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 13 times the recommended human dose based on body surface area) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of nizatidine (2,000 mg/kg/day, about 27 times the recommended human dose based on body surface area) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, an indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The considered evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day,

in pediatric patients: (see DOSAGE AND ADMINISTRATION)

Clinical Trials (Pediatric). In randomized studies, nizatidine was administered to pediatric patients for up to eight weeks, using age appropriate formulations. A total of 230 pediatric patients from 2 to 18 years of age were administered nizatidine at a dose of either 2.5 mg/kg b.i.d., or 5.0 mg/kg b.i.d., (patients 12 years and under) or 150 mg b.i.d. (12 to 18 years). Patients were required to have either symptomatic, clinically suspected or endoscopically diagnosed GERD with age-relevant symptoms. In patients 2 to 18 years of age, nizatidine was found generally safe and well-tolerated. In these studies in patients 12 years and older, nizatidine was found to reduce the severity and frequency of GERD symptoms, improve physical well-being, and reduce the frequency of supplemental antacid consumption. No efficacy in pediatric patients -12 years of age has been established. Clinal studies in patients 2 to 12 years of age with GERD, demonstrated no difference in either symptom improvements or healing rates between nizatidine and placebo or between different doses of nizatidine.

Geriatric Use—Of the 955 patients in clinical studies who were treated with nizatidine, 337 (35.3%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. 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. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see Dosage and Administration)

Adverse Reactions in Adults: Worldwide, controlled clinical trials of nizatidine included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canadia included over 2,600 patients given nizatid ne and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common

in the nizatidine group.

Incidence in Placebo-Controlled Clinical Trials in the United States and Canada—Table 7 1sts adverse events that occurred at a frequency of 1% or more among nizatidine-treated patients who participated in placebo-controlled trials. The cited figures provide some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Table 7.
Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Trials

| Body System/ Adverse Event* | Percentage of Patients Reporting Event | | | Percentage of Patients Reporting Event | |
|--------------------------------|---|----------------------|--------------------------------|---|----------------------|
| | Nizatidine (N=2,694) | Placebo (N=1,729) | Body System/ Adverse Event* | Nizatidine (N=2,694) | Placebo (N=1,729) |
| Body as a Whole | | - | Nervous | | |
| Headache | 16.6 | 15.6 | Dizziness | 4.6 | 3.8 |
| Pain | 4.2 | 3.8 | Insomnia | 2.7 | 3.4 |
| Asthenia | 3.1 | 2.9 | Abnormal dreams | 1.9 | 1.9 |
| Chest pain | 2.3 | 2.1 | Somnolence | 1.9 | 1.6 |
| Infection | 1.7 | 1.1 | Anxiety | 1.8 | 1.4 |
| Injury, accident | 1.2 | 0.9 | Nervousness | 1.1 | 0.8 |
| Digestive | | | Respiratory | | |
| Diarrhea | 7.2 | 6.9 | Rhinitis | 9.8 | 9.6 |
| Dry mouth | 1.4 | 1.3 | Pharyngitis | 3.3 | 3.1 |
| Tooth disorder | 1.0 | 0.8 | Sinusitis | 2.4 | 2.1 |
| Musculoskeletal | | | Cough, increased | 2.0 | 2.0 |
| Myalgia | 1.7 | 1.5 | Skin and Appendag | es | |
| | *** | | Rash | 1.9 | 2.1 |
| | | | Pruritus | 1.7 | 1.3 |
| | | | Special Senses | | |
| | | | Amblyopia | 1.0 | 0.9 |

*Events reported by at least 1% of nizatidine-treated patients are included

A variety of less common events were also reported; it was not possible to determine whether these were

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.
Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of nizatidine. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of nizatidine.

Cardiovascular—In clinical pharmacologous challes short enisodes of assymboratic ventricular tachvegaria.

patinice have been reported with revealed or the aniionmaintes after discontinuation of inzadurine.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered rizatidine and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients who received nizatidine and by lhose given placebo. Rare reports of gynecomastia occurred.

Hematologic—Anemia was reported significantly more frequently in nizatidine- than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urt caria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported. Vasculitis has been reported rarely. Hypersensitivity—As with other Hy-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Rare episodes of hypersensitivity reactions (eg. bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Body as a Whole—Serum sickness-like reactions have occurred rarely in conjunction with nizatidine use. Genitourinary—Reports of impotence have occurred.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Adverse Reactions (Pediatric): In controlled clinical trials in pediatric patients (age 2 to 18 years), nizatidine was found to be generally safe and well tolerated. The principal adverse experiences (> 5%) were pyrexia, nasopharyngitis, diarrhea, vomiting, irritability, nasal congestion and cough. Most adverse events were mild or moderate in severity. Mild elevations in serum transaminase (1-2 x ULN) were noted in some patients. One subject experienced a seizure by EEG diagnosis after taking Axid Oral Solution 2.5 mg/kg b.l.d. for 23 days. The adverse reactions reported for nizatidine may also occur with Axid Oral Solution.

Ore supject experienced a sezure by Eco diagnosts after landing Aud or al Solution.

Overdosage: Overdoses of nizatidine have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms—There is little clinical experience with overdosage of nizatidine in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, mesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dops and of 1,200 mg/kg in domy mg/kg in most such as the server of testal Intravenous median lethal doses in 800 mg/kg in dops and of 1,200 mg/kg, respectively. In the two 8-week pediatric exposure trials of nizatidine in 256 pediatric patients, there were no cases of deliberate overdosage. In one study of nizatidine 10 mg/kg/day, drug compliance rates up to 7.5% above 100% compliance were not associated with clinically significant adverse events.

Treatment—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference (PPR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

Dosage and Administration:

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Active Duodenal Ulcer—The recommended oral dosage for adults is 300 mg once daily at bedtime

An alternative dosage regimen is 150 mg twice daily.

Maintenance of Healed Duodenal Ulcer—The recommended oral dosage for adults is 150 mg once daily

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Gastroesophageal Beflux Disease—The recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated hearthurn is 150 mg twice daily.

Active Benign Gastric Ulcer—The recommended oral dosage is 300 mg given either as 150 mg twice daily or 300 mg once daily at bedtime. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

Each mL of Axid Oral Solution contains 15 mg of nizatidine. In adults, Axid Oral Solution may be substituted for any of the above indications using equivalent doses of the oral solution.

Pediatric Dasing—Each mL of oral solution contains 15 mg of nizatidine. Axid Oral Solution is indicated for pediatric patients 12 years of age or older, for pediatric patients 12 years of age and older, the dosage of nizatidine is 150 mg b.i.d. (2 tsp., b.i.d.)

The following dosage recommendations are provided:

Erosive Esophagitis—For pediatric patients 12 years or older, the dosage is 150 mg b.i.d. (300 mg/d). The maximum daily dose for nizatidine P0 is 300 mg/d. The dosing duration may be up to eight weeks.

Castroesophageal Reflux Disease—For pediatric patients 12 years or older, the dosage is 150 mg b.i.d. (300 mg/d). The maximum daily dose for nizatidine P0 is 300 mg/d. The dosing duration may be up to eight weeks.

Cosage Active Duodenal Ulcer, GERD, and Benign Gastric Ulcer

Creatine Clearance

Dose

20-50 mL/min

150 mg every other day

20-50 mL/min, and, based on pharmacokinetic data in patients with renal impairment, the dose for such patients should be reduced accordingly. The clinical effects of this dose reduction in patients with renal failure have not been evaluated.

Based on the pharmacokinetic data in elderly patients with renal impairment, pediatric patients with creatinine edearances of nizatid

How Supplied: Axid (nizatidine) Oral Solution 15 mg/mL is formulated as a clear, yellow, oral solution with bubble gum flavor

Bottles of 480 mL (16 fl. oz.) – NDC# 52268-147-62 Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature] and dispense in tight, light-resistant container.

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