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# Family Practice Grand Rounds

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## Herpes Simplex Encephalitis

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Madison, Wisconsin

DR. WILLIAM SCHEIBEL (*Assistant Professor of Family Medicine*): Dr. Raczek and I will review herpes-simplex encephalitis through the presentation of a mentally retarded patient whom we recently attended with this illness. We are fortunate in having two surviving sisters, Margaret and Janet, who agreed to come today. We wish to thank them for coming to our rounds to share their experiences regarding this terrible illness with us, and to discuss the importance of the family conferences held during its course.

Herpes simplex encephalitis is a viral infectious disease that produces necrosis, hemorrhage, and

edema of the brain. The mortality in untreated patients has been estimated in the literature to be 70 percent. There has been some concern recently, especially in the British literature, that the spectrum of this disease ranges from severe and rapidly progressive, to a more benign variant with a lower mortality.<sup>1</sup> The temporal lobe is most commonly involved in herpes encephalitis, and there are two postulates as to why this is so. One hypothesis, that the virus spreads from the nasopharynx along the olfactory pathway to the temporal lobe, is supported by the majority of cases being caused by herpes-simplex type I virus. Another hypothesis derives from autopsy findings, which have revealed latent herpes virus in the trigeminal nerve ganglion. It has been proposed that herpes encephalitis is due to a reactivation of this virus with subsequent spread to the temporal lobe.<sup>2</sup>

I would like to turn now to the presentation of our patient.

DR. JAMES RACZEK (*Third-year family practice resident*): Viola was a 56-year-old white woman with mild-to-moderate mental retardation secondary to phenylketonuria. On the day of admission,

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the patient fell from a chair at the breakfast table and was witnessed to have a 40- to 60-second loss of consciousness. There was no tonic or clonic activity noted, but the patient was incontinent of feces and urine. The patient awoke with intermittent confusion and lethargy. She complained of a headache and vomited twice. She was evaluated in the emergency room about an hour after the event and was asymptomatic. Her past medical history was significant for multifocal, premature-ventricular contractions, which had been noted two years earlier and had been relatively well-controlled with low-dose propranolol.

In the emergency room, the patient was alert, with a normal blood pressure and no fever. The physical examination, including the neurologic examination, was within normal limits, except for a regularly irregular pulse of 60 beats per minute. The electrocardiogram (ECG) showed ventricular bigeminy, which led us to an initial diagnosis of a syncopal episode, probably due to a Stokes-Adams attack. A complete blood count (CBC), electrolytes, calcium and glucose were determined to evaluate the possibility of a reversible seizure disorder. Serial cardiac enzymes were also determined to eliminate myocardial injury as the cause of her arrhythmia. All blood tests were normal.

The patient was admitted to the coronary care unit for monitoring, and started on intravenous (IV) lidocaine and oral quinidine to suppress the ventricular ectopy. The rhythm stabilized on the medication, and the patient was transferred from the coronary care unit to the medical floor the following morning.

On the second hospital day, the patient developed a fever to 101° F orally. That afternoon she had a seizure consisting of rhythmic movements of the right arm. Phenytoin was given intravenously to prevent further seizure activity. An electroencephalogram (EEG) and a computerized tomographic (CT) scan were ordered for early the next morning. During the evening, the patient's temperature increased to 103° F orally. A workup for septicemia was initiated, including blood and urine cultures along with a repeat CBC and urinalysis. These were all normal. A lumbar puncture was scheduled for the following morning after the EEG and CT scan.

On the third hospital day, the patient again had a seizure prior to the scheduled CT scan and be-

came obtunded. This was witnessed as a focal seizure in which there were rhythmic movements of the right face with associated lip smacking. She was treated intravenously with 10 mg of diazepam and 250 mg of phenytoin, which suppressed the seizure activity.

The CT scan was completed following the seizure and was negative. The EEG was interpreted as abnormal, demonstrating diffuse disturbance of the background activity over the left hemisphere with increased asymmetric amplitude of the brain waves in this area.

A neurologist was consulted after obtaining the CT scan and EEG. He agreed that a lumbar puncture was needed, which was done without complication. The opening pressure was normal, and the Gram stain was negative for bacteria. There were five red blood cells (RBC) and 45 white blood cells (WBC) in the cerebrospinal fluid. The WBC differential was 82 percent lymphocytes, 15 percent monocytes, and 3 percent neutrophils. The protein was 34 mg/dL and the glucose was 84 mg/dL.

The findings of the abnormal EEG, the negative CT scan, the abnormal cerebrospinal fluid, and the patient's presentation of a rapidly worsening course with focal seizures pointed toward an acute encephalitis secondary to herpes as the most probable diagnosis.

**DR. SCHEIBEL:** With the onset of fever, repetitive focal seizures, and obtundation, our working diagnosis became that of an acute encephalitis, probably herpes encephalitis. The differential diagnosis included a seizure disorder, brain abscess, brain tumor, cerebrovascular accident, and toxic or metabolic encephalopathy.

The National Institute of Allergy and Infectious Disease (NIAID) Collaborative Antiviral Study Group followed a group of patients who had findings compatible with herpes simplex encephalitis. These patients had an acute febrile encephalitis with temporal lobe signs, disorientation, evidence of localized or focal central nervous system disease, and cerebrospinal-fluid findings compatible with viral encephalitis (mononuclear pleocytosis, elevated protein, and a depressed glucose).

In this NIAID study, the diagnosis of herpes encephalitis was then confirmed by isolation of the virus from brain biopsy or autopsy specimens.<sup>3</sup> The other diagnoses that were found at the time of biopsy included acute encephalitis due to cox-

sackie virus, mumps, cryptococcus, St. Louis virus, Epstein-Barr virus, and influenza virus.

DR. WILLIAM SCHECKLER (*Associate Professor of Medicine and Family Medicine*): How large was the study population?

DR. SCHEIBEL: In this part of the NIAID study, there were 75 patients who had biopsy-proven herpes encephalitis, and 57 patients who were biopsy negative for herpes simplex virus.

The historical findings most commonly present in herpes simplex encephalitis are alteration of consciousness, fever, headache, personality change, seizures, and vomiting. The NIAID study compared these findings with the biopsy-positive and biopsy-negative groups to see whether any of these factors were significant enough to predict the diagnosis without actually performing the brain biopsy. These findings were very similar in both groups and could not be used to predict the patients with herpes encephalitis.

The most characteristic presenting signs of herpes simplex encephalitis are fever, disorientation, autonomic nervous system dysfunction, and focal neurologic findings including ataxia, hemiparesis, cranial nerve defects, visual field losses, papilledema, and seizures. The biopsy positive and biopsy negative groups were again compared, and no one sign, or combination of signs, could be factored out to make an accurate diagnosis of herpes-simplex encephalitis.

Neurodiagnostic testing is useful in herpes simplex encephalitis by identifying focal central nervous system disease. These tests include EEG, brain scan, and CT scan. In the NIAID study, a combination of clinical findings and positive neurodiagnostic tests predicted the patients with biopsy positive herpes simplex encephalitis in 83 percent of patients. However, the NIAID study also noted a 25 percent incidence of false positives using the same criteria.<sup>4</sup> This lack of specificity in diagnosing herpes simplex encephalitis has touched off considerable debate as to whether brain biopsies are necessary in all patients.<sup>5</sup>

In the NIAID study, a brain biopsy was a requirement for diagnosis. Biopsies confirmed the diagnosis in 57 percent of the suspected cases and established an alternative diagnosis in 23 percent of the same suspected cases. The complication rate of the brain biopsy was less than 2 percent.

There are, however, potential problems with

brain biopsy. First, the disease has a patchy distribution in the brain tissue; consequently, doing an open craniotomy where the necrotic brain tissue can be visualized is a better method than a needle biopsy. Second, neurodiagnostic tests may not accurately localize the most involved area of the brain, and a biopsy may consequently be negative. Last, there are also technical errors in processing the isolation of the virus, especially if biopsy specimens have to be transported to another laboratory for evaluation.<sup>6</sup>

DR. RACZEK: Because there was a strong suspicion that this was herpes simplex encephalitis, it was decided to start treatment empirically without the brain biopsy. Treatment was started with vidarabine on the third hospital day after the other available antiviral drugs, especially acyclovir, were discussed. Our neurology consultant noted that studies using acyclovir for herpes encephalitis were inconclusive, and that vidarabine had been shown to be effective for this disease; therefore, vidarabine was chosen.<sup>7,8</sup> Viral studies were obtained, and the brain biopsy was considered, but felt unnecessary because of the patient's poor condition and lack of focal abnormalities on the CT scan.

After deciding on treatment and transferring the patient into the medical intensive care unit, I met with the family members, who included both sisters, Margaret and Janet, and two members of the group home where Viola had been living. We discussed the diagnosis of herpes simplex encephalitis and what that meant. We talked about Viola's very grave prognosis and the need to re-evaluate her each day. We discussed the uncertainty of the diagnosis. Although we had considerable evidence pointing toward herpes encephalitis, we did not have a brain biopsy to confirm it. We talked about what type of support we should give the patient, including whether ventilation or full resuscitation should be used, if needed.

DR. SCHEIBEL: How was the prognosis presented to you in regard to the herpes simplex encephalitis?

JANET: It was handled very well. We felt that no information was withheld. Dr. Raczek explained what was likely to happen, and I think that probably was a big factor in our decision not to use the ventilator or resuscitate Viola should it become necessary. We were worried about resusci-

tation because of the severity of her illness and the possible consequences of her living in a vegetative state.

DR. SCHEIBEL: Do you have any suggestions regarding the family conference that Dr. Raczek held with you?

JANET: When there is a conference with a family, I think it should be in a private area or room. It was no fault of Dr. Raczek's, but there was just no place we could go initially. Whenever we did talk, we talked in the hall. There was no privacy because there was always traffic through the hall; people would stop and try to listen because everybody was terribly upset, and this was something that was very important. When we got upstairs to the neurology floor, there were conference rooms, and communication was much easier. We could think the situation through.

It also would have been easier if we had had one doctor to relate to. Initially, we had a different doctor every two days. Once we started meeting with Dr. Raczek, it was much better. It is different when you are acquainted with your family doctor. We had never met any of the doctors from the Verona Clinic, and it was hard for everybody. Things did work out very well after we got our feet on the ground and started communicating with Dr. Raczek. We had good communication lines with him. The nursing staff was terrific.

DR. SCHEIBEL: I think this really underscores the importance of the family conference. Before the first conference was held, a lot of information was being disseminated to the family at the time of rounds in the morning by different people including nursing staff, consulting neurologists, and multiple residents. Once Dr. Raczek met with the family for the first conference, a clear, more consistent report of the patient's condition could be given.

MARGARET: Thursday night (second hospital day) we did not realize how sick Viola was. I was in to see her on that afternoon. At that time she did not recognize me, or one of the ladies from the group home who was also there. We talked to her, and about 6:30 PM she did finally seem to recognize me, but we had to keep talking to her and telling her who we were. I really don't know if she did or did not know me, but she had had the seizure just prior to our coming in. At that point, I did realize there was something really strange going on.

The next day when I visited her, there was

something obviously very wrong. I just couldn't get her to react to anything. She was a cat lover, and she had a beautiful book on cats, but I was unable to get her to tell me which cats she liked on a particular page. She just lay in bed, all curled up. I would ask, "Is this the one you like?" but I couldn't get her to answer. I did call Dr. Raczek and say there was something very wrong with Viola. I don't believe she ever recognized us after that point; that characteristic smile of hers wasn't there.

JANET: Meeting new doctors in the middle of an illness is difficult. Viola had been a patient of Verona Clinic prior to her illness, but we had never met any of the doctors. When I came in the first afternoon, I did meet Dr. Bondow (graduating family practice resident) and I did talk to him. Then on the evening of the first seizure, I met Dr. Raczek, who eventually took over the care of Viola. When there are guardians and other important family members who might be involved in a patient's care, it might be worthwhile for the doctor to make some effort to meet them before an illness occurs. We have another sister who is at the same group home, and she also goes to the Verona Clinic. I am her guardian, and I do think, now that we know some of the doctors out there, it will be easier to communicate if she were to get ill. Up to this time, we had not really had any need for any type of contact with the clinic. We kept in contact with the home; we went to see our sisters regularly and brought them home frequently for a day.

DR. LYNN PHELPS (*Clinic Director and Associate Professor of Family Medicine*): Were the people from the home where your sisters were staying involved with the initial family conference too?

JANET AND MARGARET: Yes, all along.

DR. PHELPS: Was that helpful?

MARGARET: At that time, we thought it was.

DR. SCHEIBEL: That takes on more significance as the presentation continues. Treatment of Viola was begun with vidarabine, 15 mg/kg/d infused over 12 h/d. In the NIAID Collaborative Antiviral Study Group, the use of vidarabine was shown to decrease mortality in herpes simplex encephalitis from the previously mentioned 70 percent to about 40 percent in one year.<sup>3</sup> In this study, the drug was continued for 10 days if the brain

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**Azo Gantrisin®**

Each tablet contains 0.5 Gm sulfisoxazole/Roche and 50 mg phenazopyridine HCl.

Before prescribing, please consult complete product information, a summary of which follows:

**INDICATIONS:** Initial treatment of uncomplicated urinary tract infections caused by susceptible strains of *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Proteus mirabilis*, *Proteus vulgaris* and *Staphylococcus aureus* when relief of pain, burning or urgency is needed during first 2 days of therapy. Azo Gantrisin treatment not to exceed 2 days. Evidence lacking that sulfisoxazole plus phenazopyridine HCl better than sulfisoxazole alone after 2 days. Treatment beyond 2 days should only be continued with Gantrisin (sulfisoxazole/Roche). (See DOSAGE AND ADMINISTRATION.) **Important Note:** Coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response. With ongoing therapy, add aminobenzoic acid to culture media. Increasing resistance of organisms may limit sulfonamide usefulness. As identical doses produce wide variations, measure blood levels in patients receiving sulfonamides for serious infections: 12 to 15 mg/100 ml is optimal; adverse reactions are more frequent above 20 mg/100 ml.

**CONTRAINDICATIONS:** Children under 12; known sensitivity to either component; pregnancy at term and during nursing period; in glomerulonephritis, severe hepatitis, uremia and pyelonephritis of pregnancy with gastrointestinal disturbances.

**WARNINGS:** Sulfonamides are bacteriostatic; organisms causing common infections are often resistant. Sulfas won't eradicate group A streptococci or prevent sequelae like rheumatic fever and glomerulonephritis. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Perform blood counts and renal function tests.

**PRECAUTIONS: General:** Use with caution in patients with impaired renal or hepatic function, severe allergy, bronchial asthma. Hemolysis may occur in glucose-6-phosphate dehydrogenase-deficient individuals.

The more soluble sulfonamides are associated with fewer renal complications. Maintain adequate fluid intake to prevent crystalluria and stone formation.

**Information for Patients:** Maintain adequate fluid intake; urine will turn reddish-orange.

**Laboratory Tests:** Perform urinalysis with careful microscopic examination at least once a week and regular blood counts after 2 weeks therapy; measure blood levels in patients with serious infection (see INDICATIONS). **Drug Interactions:** Sulfonamides may displace oral anticoagulants from plasma protein binding sites, increasing anticoagulant effect. Can also displace methotrexate. **Drug Laboratory Test Interactions:** May affect liver function tests in hepatitis.

**Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Azo Gantrisin has not undergone adequate trials relating to carcinogenicity; each component, however, has been evaluated separately. Rats appear especially susceptible to goitrogenic effects of sulfonamides; long-term administration has resulted in thyroid malignancies in this species. Long-term administration of phenazopyridine HCl has induced neoplasia in rats (large intestine) and mice (liver). No association between phenazopyridine HCl and human neoplasia reported; adequate epidemiological studies have not been conducted. **Mutagenesis:** No studies available. **Impairment of Fertility:** The components of Azo Gantrisin have been evaluated in animal reproduction studies. In rats given 800 mg/kg/day sulfisoxazole, there were no effects on mating behavior, conception rate or fertility index. Fertility was not affected in a two-litter study of rats given 50 mg/kg/day phenazopyridine.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. The components of Azo Gantrisin have been evaluated. At 800 mg/kg/day sulfisoxazole was nonteratogenic in rats and rabbits, with no perinatal or postnatal effects in rats. In two other studies, cleft palates developed in rats and mice after 500 to 1000 mg/kg/day sulfisoxazole. No congenital malformations developed in rats given 50 mg/kg/day phenazopyridine. As there are no satisfactory animal or human studies, it is not known whether Azo Gantrisin can cause fetal harm or affect reproduction capacity. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects, Nursing Mothers and Pediatric Use:** See CONTRAINDICATIONS.

**ADVERSE REACTIONS: Allergic:** Anaphylaxis, generalized allergic reactions, angioneurotic edema, arteritis and vasculitis, myocarditis, serum sickness, conjunctival and scleral injection, periarteritis nodosa, systemic lupus erythematosus. **Cardiovascular:** Tachycardia, palpitations, syncope, cyanosis. **Dermatologic:** Rash, urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, photosensitivity. **Endocrine:** Goiter production, diuresis, hypoglycemia. Cross-sensitivity with some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents may exist. **Gastrointestinal:** Nausea, emesis, abdominal pain, anorexia, diarrhea, glossitis, stomatitis, flatulence, salivary gland enlargement, G.I. hemorrhage, pseudomembranous enterocolitis, melena, pancreatitis, hepatic dysfunction, jaundice, hepatocellular necrosis. **Genitourinary:** Crystalluria, hematuria, BUN and creatinine elevation, nephritis and toxic nephrosis with oliguria and anuria, acute renal failure, urinary retention. **Hematologic:** Leukopenia, agranulocytosis, aplastic anemia, thrombocytopenia, purpura, hemolytic anemia, anemia, eosinophilia, clotting disorders including hypoprothrombinemia and hypofibrinogenemia, sulfhemoglobinemia, methemoglobinemia. **Musculoskeletal:** Arthralgia, chest pain, myalgia. **Neurologic:** Headache, dizziness, peripheral neuritis, paresthesia, convulsions, tinnitus, vertigo, ataxia, intracranial hypertension. **Psychiatric:** Psychosis, hallucinations, disorientation, depression, anxiety. **Miscellaneous:** Edema (including periorbital), pyrexia, drowsiness, weakness, fatigue, lassitude, rigors, flushing, hearing loss, insomnia, pneumonitis.

**OVERDOSAGE: Signs:** Anorexia, colic, nausea, vomiting, dizziness, drowsiness, unconsciousness; possibly pyrexia, hematuria, crystalluria. Blood dyscrasias and jaundice may occur later. **Treatment:** Institute gastric lavage or emesis; force oral fluids; administer intravenous fluids if urine output is low with normal renal function. Monitor blood counts and appropriate blood chemistries, including electrolytes. In cyanosis, consider methemoglobinemia and treat with intravenous 1% methylene blue. Institute specific therapy for blood dyscrasias or jaundice.

**DOSAGE AND ADMINISTRATION:** Azo Gantrisin is intended for the acute, painful phase of urinary tract infections. The recommended dosage in adults is 4 to 6 tablets initially, followed by 2 tablets four times daily for up to 2 days. Treatment with Azo Gantrisin should not exceed 2 days. Treatment beyond 2 days should only be continued with Gantrisin (sulfisoxazole/Roche).

**HOW SUPPLIED:** Tablets, each containing 0.5 Gm sulfisoxazole/Roche and 50 mg phenazopyridine HCl—bottles of 100 and 500.

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biopsy was positive and stopped after 5 days if the biopsy was negative. The study also found that 32 percent of surviving patients returned to normal (ie, returned home from the hospital with only minor disabilities), 17 percent of patients left the hospital with moderate disability (ie, they were home, performing activities of daily living, but were hampered by neurologic deficits), and 11 percent of patients were categorized as having severe disability (ie, they remained institutionalized, requiring supportive care).

Several factors are predictive of the outcome in herpes simplex encephalitis. The level of consciousness of the patient at the start of vidarabine therapy is an important variable. Lethargic patients have a lower mortality than semicomatose patients who have a lower mortality than comatose patients at the start of therapy. Viola was semicomatose at the start of therapy. Age is also an important predictor. If the patient is younger than 30 years old, the prognosis is better than if they are older than 30 years. Viola was 56 years. In the NIAID study, the patient who was lethargic at the start of vidarabine therapy was also younger than 30 years had a 90 percent change of survival and a 70 percent chance of returning to normal functioning. A semicomatose patient older than age 30 years, which is the group Viola fits into, had less than a 40 percent survival rate, and none of the survivors met the criteria for normal functioning. It is also interesting that the final outcome cannot be predicted immediately after treatment in this disease, since 50 percent of survivors can continue to improve in the first year.

Several letters published in *Lancet* question attributing the 30 percent improvement in mortality to just the vidarabine therapy.<sup>1</sup> They point out that the study was not double blind or controlled, and that one third of the patient population were subjects younger than 19 years of age. They further hypothesized that there may be a spectrum of this disease with the 70 percent mortality occurring in the older patients. Complications of vidarabine therapy include an erythematous, nonpruritic rash, diarrhea, decreased white blood count, decreased platelets, and increased liver enzymes. There is also a theoretic concern that cerebral edema or congestive heart failure could be worsened as a result of the large amounts of intravenous fluids required to give the drug over 10 hours



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each day. Another concern raised was that toxicity is probably increased by renal and hepatic insufficiency as well.

DR. RACZEK: Two days after starting the vidarabine therapy, the patient developed respiratory distress secondary to an inability to handle secretions. Intubation was performed to permit suctioning of the secretions, but a ventilator was not used. Culture of the endotracheal secretions grew out *Staphylococcus aureus*, and the patient was begun on nafcillin intravenously for the staphylococcal pneumonia. This occurred on the weekend and many caretakers were involved. The family felt they were getting diverse messages from the various caregivers and asked that one person be appointed as spokesman. I assumed this role.

One of the group home employees felt the family were making decisions that were not in the best interest of Viola. I reassured this person that the family members were making decisions in conjunction with hospital clergy, nursing service, and me. I told her I felt the decisions that had been made were quite appropriate. This person disagreed with me and consulted the Advocates for Retarded Citizens (ARC). ARC began an investigation of the case and contacted Margaret. The investigating lawyer contacted the hospital, myself, and the neurologist. He knew the specific details of the patient's history and hospital course, which surprised me, as I thought this was confidential information. His major question was whether I was comfortable with the decisions the family was making. I reassured him that I was. The neurologist also echoed these sentiments. The lawyer did not feel any further investigation or action was indicated.

I scheduled another family conference including both sisters and the two group home caretakers who had been most involved with Viola when she lived there. I hoped to use the family conference to defuse the tension between the family and the group home caretakers. At this point, Margaret requested that all information be given only to family members, who would then keep people in the group home informed.

DR. SCHEIBEL: I wonder whether you could again describe your feelings at the point when you were already obviously distressed by your sister's serious illness and were having some of your decisions brought into question.

MARGARET: I was totally put out because until then the people at the home had reassured me they thought I was making the right decisions. Then all at once I received this call questioning my intentions and asking whether I was too emotionally involved to make correct decisions.

JANET: Following that call, we asked our two other brothers and sister to meet with us. Margaret asked all of us whether we felt she had made any wrong decisions through the whole illness. We all assured her that we backed her completely. She wanted to be sure that she had the family backing her. We then talked to Dr. Raczek, who reassured us that we were making the right decisions, also. We felt the doctors were advising us in the direction we were taking. We had also talked with the clergy as well. At that point, Margaret felt reassured that she had made the right decision and did not want to change it. The family conference did help tremendously to clear the air. Our relationship with the group home personnel, however, is strained. Although we have seen the people from the home on several occasions, things are not like they were. It is a difficult situation with our other sister still living at the group home. We put a lot of thought into that situation and decided to leave it as is right now. There is a biyearly conference with the home personnel at the school, and we are awaiting that conference to see if things have settled down by then.

DR. BALDWIN LLOYD (*Clinic Director and Associate Professor of Family Medicine*): Can you expand on how the group home personnel's thoughts differed from yours, and what decision they would have made?

MARGARET: They continued to think that Viola did respond to their presence in the room and seemed to think that she still recognized them. They, therefore, felt that she really did need a ventilator over the weekend. Once I had made my decision not to use a ventilator, I still hoped and prayed she would get better, but I never doubted my decision again. I thought that when the Lord wants her, He is going to take her, and I am not the one who is going to have to make a decision to pull the plug on a ventilator.

DR. SCHEIBEL: Control of secretions was much better after the patient was intubated, and the patient's blood gases did not support the use of the ventilator at this point.

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**References:**

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

**BRIEF SUMMARY****PROCARDIA® (nifedipine) CAPSULES**

For Oral Use

**INDICATIONS AND USAGE:** I. **Vasospastic Angina:** PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. **Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

**CONTRAINDICATIONS:** Known hypersensitivity reactions to PROCARDIA.

**WARNINGS: Excessive Hypotension:** Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

**Increased Angina:** Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

**Beta Blocker Withdrawal:** Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

**Congestive Heart Failure:** Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

**PRECAUTIONS: General: Hypotension:** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

**Peripheral edema:** Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Drug interactions:** Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

**ADVERSE REACTIONS:** The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation about 2% and syncope in about 0.5%. Syncopal episodes did not occur in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

**Laboratory Tests:** Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

**HOW SUPPLIED:** Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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JANET: At every conference we had with Dr. Raczek, we asked him that question; he reassured us that her critical condition was not due to the lack of a ventilator.

DR. RACZEK: Part of the problem for the people at the home was the initial fragmentation of information being given to them. They were interpreting the bits and pieces of information differently than we were.

MARGARET: At that time, I was in agreement with sharing with the group home caretakers any information that we were receiving. We know they took a very keen interest in their patients and were as concerned as we were for Viola's health. Viola had been living with them for the past five years. If the situation ever arose again, I would do a lot of thinking before having other people present for information regarding a sick family member.

DR. SCHEIBEL: Their concern was that some of the decision making was on the basis of Viola's underlying mental retardation.

JANET and MARGARET: That was never our thinking.

MARGARET: If I were ever in this situation, I would hope people would make the same decisions I did.

DR. MARC HANSEN (*Professor of Pediatrics and Family Medicine*): This situation shows the importance of discussing possibilities in advance of serious illness and supports developing a critical care plan for nursing home patients. It is helpful to talk about what would happen, and how decisions would be made when a member of the nursing home or group home became ill. A critical-care plan may be something that is still necessary with regard to your other sister.

JANET: If our other sister were to become critically ill, I would want to make the decisions as her guardian. If she were to be critically ill, I would agree with people from the group home visiting her, but I would want all medical information to them through me, rather than direct access through the doctor.

DR. STANLEY LIVINGSTON (*Third-year family practice resident*): Do you think, had the group home staff been present when the therapeutic options were explained, they would have felt better about the decisions that were made?

DR. RACZEK: I don't know. The decisions were made over the weekend, when I was out of

town. Their presence might have been beneficial.

The remainder of Viola's hospital course was one of slow deterioration leading to her death. On day 7 of vidarabine therapy, the patient developed leukopenia ( $900/\text{mm}^3$ ) and a thrombocytopenia ( $45,000/\text{mm}^3$ ). At that point, the vidarabine was discontinued. Sequential EEGs were performed during the hospital course and were all consistent with herpes encephalitis, but not diagnostic. A CT scan was repeated five days after the presumptive diagnosis and showed marked left hemispheric edema consistent with herpes encephalitis. At this point, dexamethasone and mannitol were added, but they had no effect on the patient's course. These drugs were consequently discontinued after three days. At this time, a corneal ulcer was noted, but a culture failed to show herpes. The patient also developed hypernatremia, which was treated with hypotonic intravenous solutions. On the final day of hospitalization, the patient developed pulmonary edema and expired.

DR. SCHEIBEL: Neurodiagnostic testing attempts to identify focal central nervous system disease. The EEGs usually show localized spikes or slow waves with high-voltage complexes from the temporal lobe of a semiperiodic nature.<sup>9</sup> Viola's EEG did not show these classic findings, but did localize to the temporal lobes. A technetium brain scan usually shows enhanced unilateral uptake of radionucleotide in the involved area of the brain. The CT scan usually will show localized edema, low-density lesions, and hemorrhage, if present. The laboratory evaluation for making the diagnosis of herpes simplex encephalitis includes cultures of herpes virus from either brain biopsy or autopsy material.

In research laboratories, electron microscopy has been used for detection of the herpes-virus particles. Fluorescent antibody stains for herpes virus antigens appear to be useful and are often used on the brain biopsy specimens. This test has the advantage of taking only a few hours to perform. Serum antibody studies are useful if they show a fourfold or greater increase. A great deal of research is being done on evaluating cerebrospinal fluid for antibodies or other byproducts of the herpes virus and holds promise for a more rapid and less invasive diagnosis of this disease in the future.<sup>10</sup> Cerebrospinal fluid cultures have been disappointing, and viruses have been isolated in

less than 4 percent of cases. The peripheral excretion of virus appears to be similar in both the biopsy positive and biopsy negative groups in the NIAID studies.

DR. RACZEK: An autopsy was performed on this patient, and the final anatomical diagnosis was herpes simplex encephalitis involving the left temporal parietal cerebrum. Sections through this area showed extensive areas of necrosis and positive antigen staining for herpes virus. The patient was also found to have a right lower lobe bronchopneumonia with abscess formation that grew *Staphylococcus aureus* on culture. Thrombosis of the renal vein and veins to the adrenal medulla were also present.

DR. SCHEIBEL: Any final comments?

MARGARET: We were pleased with Viola's care, but wish to emphasize the initial confusion as a result of her having so many doctors.

DR. LLOYD: Would it have been better from your point of view had all of the consultants talked to one physician and he talked to you, rather than receiving messages from several people?

MARGARET and JANET: Yes, and that is what happened after Dr. Raczek had the family conference with us.

DR. SCHEIBEL: I want to thank Janet and Margaret for attending this conference today. I hope it was of value to both of you.

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