Vancomycin Crosses Placental Barrier, Study Finds

BY SHERRY BOSCHERT

San Francisco Bureau

MONTEREY, CALIF. — The first in vivo study of the pharmacokinetics of IV vancomycin in pregnant women found that it crosses the placental barrier, and that the dose recommended for prophylaxis against neonatal group B streptococcus infection may be too high, Dr. Joann Laiprasert said.

Penicillin is the first-line choice for pro-

phylactic treatment of pregnant women colonized with group B streptococcus (GBS) at 35-37 weeks' gestation. For women with penicillin allergy who have a high risk for anaphylaxis, clindamycin is the preferred drug, but 15%-30% of GBS isolates are resistant to clindamycin. Erythromycin should not be used in this situation because it has a similar resistance pattern and its passage through the placenta is incomplete.

Vancomycin is recommended for pregnant women at high risk of anaphylaxis from penicillin who have clindamycin-resistant GBS, she explained at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

In the study, 13 healthy pregnant women with no indications for antibiotics volunteered to receive 1 g of intravenous vancomycin. Seven women (54%) did not get the full dose because they developed symptoms of Red Man's syndrome, and the drug was stopped. Despite not getting the full dose, all women and fetuses had serum levels of vancomycin above the 1 mcg/mL breakpoint for effective prophylaxis against neonatal GBS, reported Dr. Laiprasert of the University of Michigan, Ann Arbor, and her associates.

The investigators extrapolated the data to model the effects if all women had received 1-g doses and calculated that this would produce supertherapeutic serum levels of the drug in the mother and the fetus. A second model in which all women received only 500 mg of vancomycin still would have resulted in therapeutic levels in maternal and fetal compartments.

The first four women in the study received the drug in 60-minute infusions, and an interim analysis found that three of them

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(75%) developed symptoms of Red Man's syndrome: pruritus, shortness of breath, rash. or hypotension. For the following nine patients, the infusion duration was lengthened to 90 minutes, and four of them (44%) de-

veloped symp-

toms of Red Man's syndrome.

One woman required treatment with saturated oxygen after developing a moderately severe reaction with symptoms of hypotension, shortness of breath, and oxygen desaturation. Investigators stopped the study after that, with enough data to draw conclusions about vancomycin's pharmacokinetics. Therapeutic drug levels were seen in fetal serum within 30 minutes after completing the 90-minute infusion (120 minutes after starting the infusion) and persisted for 8 hours.

Because less than the recommended 1-g dose of vancomycin produced therapeutic serum levels and because Red Man's syndrome was so common, a 500-mg dose should be considered adequate, Dr. Laiprasert suggested. A slower infusion rate also may be important for safe administration of vancomycin during pregnancy. Redosing vancomycin at 12-hour intervals seems reasonable if needed, she added.

The investigators collected amniotic fluid samples and plan to study them to improve understanding of the metabolism of vancomycin in the fetal circulation.

Dr. Mark D. Pearlman, one of Dr. Laiprasert's associates in the study, commented after her talk that using a lower dose of vancomycin in these patients makes sense. Other treatment options also need to be studied for women with clindamycin-resistant GBS who are at high risk for anaphylaxis from penicillin, added Dr. Pearlman of the university.

We really need to pressure the FDA and others to start to look at other non-βlactams that are active against GBS, to have alternatives to vancomycin," he said. "There are a whole host of newer, extended-spectrum, gram-positive drugs that have great activity against clindamycin-resistant GBS.'



ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

IDENTIFY BY DEATH REPORTED TO INVERSE THE MISK OF ENDUME HARL CARKENUMA. Three independent, case controlled studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incident rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

the last decade.

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed, on at least a semi-annual basis, to determine the need for continued therapy. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or reoccurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignan-

... here is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic strogens at equi-estrogenic doses.

INDICATIONS AND USAGE VAGIFEM is indicated for the treatment of atrophic vaginitis.

CONTRAINDICATIONS

The use of VAGIFEM is contraindicated in women who exhibit one or more of the following:

1. Known or suspected breast carcinoma.

2. Known or suspected breast carcinoma.

3. Abnormal genital bleeding of unknown etiology.

4. Known or suspected pregnancy (see PRECAUTIONS).

5. Pophyria.

6. Pophyria.

8. Hypersensitivity to any VAGIFEM constituents.

- Porphyria.
 Hypersensitivity to any VAGIFEM constituents.
 Active thrombophlebitis or thromboembolic disorders.
 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast malignancy).

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WARNINGS

1. Induction of malignant neoplasms.

1. Induction of malignant neoplasms.

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase risk of carcinoma of the endometrium in humans (see Boxed Warning). At the present time there is no antiferatory evidence that estrogens given to

the endometrium in humans (see Boxed Warning). At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent long-term follow-up of a single physician's practice has raised this possibility. Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breat ules, fibrocystic disease, or abnormal mammograms.

Galiblauder disease.
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3. Effects similar to throse caused by estrogen-progestogen oral contraceptives.

There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogens used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or obreast cancer are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer.

a. Thromboembolic disease. It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophelbeits, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug. An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. While an increased risk of thromboembolism and thrombotic disease in postmenopausal users of estrogens has not been found, this does not rule out the possibility that such an increase may be present, or that subgroups of women who have underlying risk factors, or who are receiving large doses of estrogens, may have increased risk. Therefore, estrogens should not be used (excent in treatment of malignancy)

risk.

b. Hepatic adenoma. Benign hepatic adenomas appear to be associated with the oral contraceptives. Although benign, and rare, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The relationship of this malignancy to these drugs is not known at this time.

c. Elevated blood pressure. Women using oral contraceptives sometimes experience increased blood pressure which, in most cases, returns to normal on discontinuing the drug. There is now a report that this may occur with the use of estrogens in the menopause and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. Elucose blorance. A worsening of glucose tolerance has been observed in a significant percentage of patients on

A. Glucose tolerance. A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while using

esurgeries.

A. Hypercalcemia.

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastas if this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5. Rare Event: Trauma induced by the VAGIFEM applicator may occur, especially in patients with severely atrophic vaginal mucosa.

atrophic vaginal mucosa.

PRECAUTIONS

A. General Precautions

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy.

The pretreatment and periodic physical examinations should include special references to blood pressure, breast, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogens should not be prescribed for longer than one year without another physical exam being performed.

2. Fluid retention—Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epileps, migraine, and cardiac and renal dysfunction, require careful observation.

2. Familia! Hunertinonroteinemia—Estrogen therapy may be associated with massive elevations of plasma

- Familial Hyperflipoproteinemia—Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabulism
- Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.
- So. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients.

 6. Preexisting uterine leiomyomata may increase in size during estrogen use.

 7. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

- 8. Patients with a history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

 9. Estrogens may be poorty metabolized in patients with impaired liver function and should be administered with caution in such patients.

 10. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

 11. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not yet complete.

 12. Insertion of the VAGIEFM applicator—Patients with severely atrophic vaginal mucosa should be instructed to exercise care during insertion of the applicator. After gynecological surgery, any vaginal applicator should be used with caution and only if clearly indicated.

 13. Vaginal infection—Vaginal infection is generally more common in postmenopausal women due to the lack
- caution and only if clearly indicated.
 3.1 Vaginal infection—Vaginal infection is generally more common in postmenopausal women due to the lack of normal flora seen in fertile women, especially lactobacilla; hence the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial therapy before initiation of VAGIFEM therapy.
- Information for the Patient full prescribing information, INFORMATION FOR PATIENTS.

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Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogens:

a. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin III; increased norepinephrine induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T₄ by column, or T, by radioimmunoassay. Free T₄ resin uptake is decreased, reflecting the elevated TBG, free T₄ concentration is unaftered.

- c. Impaired glucose tolerance.

e. Reduced serum folate concentration. f. Increased serum triglyceride and phospholipid concentration.

D. Carcinogenesis, Mutagenesis and Impairment of Fertility
Long term continuous administration of natural and synthetic estrogens in certain animal species
increases the frequency of carcinomas of the breast, uterus, vagina and liver
see CONTRAINDICATIONS AND WARNINGS).

E. Pregnancy Category X

Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Treatment with diethytstilbe-strol (DES) during pregnancy has been associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus, and possibly other birth defects. The use of DES during pregnancy has lose hear associated with a subsequent increased risk of breast cancer in the mothers.

Vagifem

IPV QDx2 weeks,

vaginal tablets

also been associated when a succession of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of contraction hreast engorgement.

G. Pediatric Use Safety and effectiveness in pediatric patients have not been established.

H. Geriatric Use

Clinical studies of VAGIFEM did not include sufficient numbers of subjects aged 65 and over to determine whether the respond differently from younger subjects, 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.

Adverse events generally have been mild: vaginal spotting, vaginal discharge, allergic reaction and skin rash. Adverse events with an incidence of 5% or greater are reported for two comparative trials. Data for patients receiving either VAGIFEM or placebo in the double blind study and VAGIFEM in the open label comparator study are listed in the following 2 tables, respectively.

ADVERSE EVENTS REPORTED IN 5% OR GREATER NUMBER OF PATIENTS RECEINING VAGIFEM IN THE PLACEBO CONTROLLED TRIAL

ADVERSE EVENT	VAGIFEM % (n=91)	Placebo % (n=47)
Headache	9	6
Abdominal Pain	7	4
Upper Respiratory Tract Infection	5	4
Genital Moniliasis	5	2
Back Pain	7	6

ADVERSE EVENTS REPORTED IN 5% OR GREATER NUMBER OF PATIENTS RECEINING

ADVERSE EVENT	VAGIFEM % (n=80)	
Genital Pruritus	6	
Headache	10	
Upper Respiratory Tract Infection	11	

Other adverse events that occurred in 3-5% of VAGIFEM subjects included: allergy, bronchitis, dyspepsia, haematuria, hot flashes, insomnia, pain, sinusitis, vaginal discomfort, vaginitis. A causal relationship to VAGIFEM has not

OVERDOSAGE

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Numerous reports of ingestion of large doses of estrogen containing oral contraceptives by young children indicate that acute serious ill effects do not occur. Overdosage with estrogens may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE ANN ADMINISTRATION

VAGIFEM is gently inserted into the vagina as far as it can comfortably go without force, using the supplied applicator.

Initial dose: One (1) VAGIFEM tablet, inserted vaginally, once daily for two (2) weeks. It is advisable to have the patient administer treatment at the same time each day.

Maintenance dose: One (1) VAGIFEM tablet, inserted vaginally, twice weekly.

Paintenance dose: One (1) VAGIFEM tablet, inserted vaginally, twice weekly.

The need to continue therapy should be assessed by the physician with the patient. Attempts to discontinue or taper medication should be made at three to six month intervals.

HUW SUPPLIED

Each NAGIFEM® (estradiol vaginal tablets), 25 µg is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contains 8 or 18 applicators with inset tablets.

8 Applicators NDC 0169-5173-03

18 Applicators NDC 0169-5173-04

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

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Reference: 1. Rioux JE, Devlin MC, Gelfand MM, Steinberg WM, Hepburn DS. 17β-Estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to refleve menopausal atrophic vaginitis. *Menopause*. 2000;7:156-161.

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