

Clinical Trials Need Minority Patients to Close Gap

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NEW YORK — Racial disparities in access to health care will disappear only when adequate and representative samples of minorities participate in clinical trials, Winston Price, M.D., said at the annual meeting of the National Medical Association.

That disparities in delivery of health care exist is not in question. The Institute of

Medicine report "Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare" revealed the extent of the problem, showing that disparities remain even after adjustment for factors such as insurance coverage and socioeconomic status.

But a widespread mistrust of the U.S. health care system among minorities—not least because of past abuses such as the Tuskegee Syphilis Study, in which blacks went untreated for many years despite the availability of effective therapy—has led to

an unwillingness among African Americans to participate in the clinical trials that might directly benefit their own health.

An increasing understanding of genetic differences and racial differences in response to medications now makes it imperative that minorities be included and their needs addressed in the drug development process, said Dr. Price of the State University of New York Health Science Center, Brooklyn.

The experience with BiDil, a fixed-dose

combination of isosorbide dinitrate and hydralazine approved specifically for the treatment of heart failure in black patients, shows it can be done (July 2005, page 1).

"You had 1,050 African Americans who enrolled in the study, and the attrition rate was zero," Dr. Price, who is also president of the NMA, said in a press briefing. "Every single one stayed with that study until completion. The drug was approved by the Food and Drug Administration on June 23, not because it was the right thing to do but because it was pure science and evidence based. All we're asking for is parity."

Other model programs also are demonstrating that blacks can be recruited successfully, Christopher L. Edwards, Ph.D., said at the briefing.

Programs that are successful tend to be well entrenched in the community; they have significant outreach and education and strong, ongoing relationships with local organizations such as churches and fraternities, Dr. Edwards said.

They do not pressure potential study participants, but rather provide information and allow patients to process the information at home and respond to the investigators when they are ready, he said.

Successful investigators are available to the community not only when recruiting; they are able to articulate the tangible benefits of participation, not only for patients themselves but also for future generations. Dr. Edwards' program in the department of psychiatry at Duke University Medical Center, Durham, N.C., is an example.

"We make ourselves available for interviews on television, religious radio, and pop radio. In one creative marketing plan, we placed advertisements for one of our genetic studies on the side of 20 city buses, and have seen a significant number of patients responding," he said.

The overall strategy of information dissemination is to go where the patients are, and not to rely on them to come to us, he said. "With the bus advertisements, the demographic we were recruiting was reliant on public transportation," he added. And the advertisements provided phone numbers, not e-mail addresses or Web sites because these would not be particularly helpful for a population that doesn't own computers.

In the Duke program, the relevant stakeholders are at the table when recruiting programs are being designed. "If we are recruiting college students, we had students who sat on review panels and advisory boards to give us guidance as to what they would respond to, how, and in what setting," Dr. Edwards said.

Another panel member, Rahn K. Bailey, M.D., said that throughout his career he has been interested in issues such as differences in drug metabolism between African Americans and other patients. For example, about 40% of black patients are slow or intermediate metabolizers of many psychiatric medications, said Dr. Bailey of the department of psychiatry and human behavior, University of Texas, Houston, and chair of the NMA psychiatry and behavioral sciences section. ■

BRIEF SUMMARY

ADOXA[®] Pak[™] 1/100 mg **ADOXA[®] Pak[™] 2/100 mg**
DOXYCYCLINE TABLETS

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline tablets and other antibacterial drugs, doxycycline tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

In severe acne, doxycycline may be useful adjunctive therapy.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

PRECAUTIONS

General: Prescribing doxycycline tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Information for Patients: Patients should be counseled that antibacterial drugs, including doxycycline tablets, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When doxycycline tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by doxycycline tablets or other antibacterial drugs in the future.

Drug Interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and iron-containing preparations.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of doxycycline have not been conducted.

However, there has been evidence of oncogenic activity in rats in studies with related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy: Teratogenic Effects. Pregnancy Category D: There are no adequate and well-controlled studies on the use of doxycycline in pregnant short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure.

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline.)

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age¹.

Labor and Delivery: The effect of tetracyclines on labor and delivery is

unknown.

Nursing Mothers: Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown². Because of the potential for adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: See WARNINGS and DOSAGE AND ADMINISTRATION sections.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See DOSAGE AND ADMINISTRATION.)

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. No abnormalities of thyroid function are known to occur.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life, and it would not be of benefit in treating cases of overdosage.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every 6 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For pediatric patients over 100 pounds the usual adult dose should be used.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.) If gastric irritation occurs, doxycycline may be given with food. Ingestion of a high fat meal has been shown to delay the time to peak plasma concentrations by an average of one hour and 20 minutes. However, in the same study, food enhanced the average peak concentration by 7.5%, and the area under the curve by 5.7%.

HOW SUPPLIED

Doxycycline Tablets 100 mg are a yellow, film coated, round, biconvex tablet, debossed "B" on one side and "729" on the other side. Each tablet contains doxycycline monohydrate equivalent to 100 mg of doxycycline. They are supplied as follows:

ADOXA[®] Pak[™] 1/100 mg (31 tablets)	NDC 10337-802-03
ADOXA[®] Pak[™] 2/100 mg (60 tablets)	NDC 10337-802-06

1. Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press; 2000: 149-195.
2. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.

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