Pregnancy

Pregnancy Category C

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to mating through weaning, maternal toxicity was observed at 0.3 times the MRHD, based on body surface area comparisons; mg/m^2.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons: mg/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

Nursing Mothers

It is not known whether fenofibrate is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fenofibrate, a decision should be made whether to discontinue nursing or administration of fenofibrate taking into account the importance of the drug to the lactating woman.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. However, elderly patients have a higher incidence of renal impairment, such that dose selection for the elderly should be made on the basis of renal function. Elderly patients with normal renal function should require no dose modifications.

ADVERSE REACTIONS

Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg TRICOR.
** Significantly different from Placebo.

Additional adverse events reported during post-marketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

Body as a Whole

Accidental injury, allergic reaction, chest pain, cyst, fever, hernia, infection, malaise and pain (unspecified).

Cardiovascular System

Angina pectoris, arrhythmia, atrial fibrillation, cardiovascular disorder, coronary artery disorder, electrocardiogram abnormal, extrasystoles, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, tachycardia, varicose vein, vascular disorder, vasodilatation, venous thromboembolic events (deep vein thrombosis, pulmonary embolus) and ventricular extrasystoles.

Digestive System

Anorexia, cholecystitis, cholelithiasis, colitis, diarrhea, duodenal ulcer, dyspepsia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, jaundice, liver fatty deposit, nausea, pancreatitis, peptic ulcer, rectal disorder, rectal hemorrhage, tooth disorder and vomiting.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Anemia, ecchymosis, eosinophilia, leukopenia, lymphadenopathy, and thrombocytopenia.

Laboratory Investigations

Alkaline phosphatase increased, bilirubin increased, blood urea nitrogen increased, serum creatinine increased, gamma glutamyl transpeptidase increased, lactate dehydrogenase increased, SGOT and SGPT increased.

Metabolic and Nutritional Disorders

Edema, gout, hyperuricemia, hypoglycemia, peripheral edema, weight gain, and weight loss.

Musculoskeletal System

Arthralgia, arthritis, arthrosis, bursitis, joint disorder, leg cramps, myalgia, myasthenia, myositis, rhabdomyolysis and tenosynovitis.

Nervous System

Anxiety or nervousness, depression, dizziness, dry mouth, hypertonia, insomnia, libido decreased, neuralgia, paresthesia, somnolence and vertigo.

Respiratory System

Allergic pulmonary alveolitis, asthma, bronchitis, cough increased, dyspnea, laryngitis, pharyngitis, pneumonia and sinusitis.

Skin and Appendages

Acne, alopecia, contact dermatitis, eczema, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, nail disorder, photosensitivity reaction, pruritus, rash, sweating, skin disorder, skin ulcer and urticaria.

Special Senses

Abnormal vision, amblyopia, cataract specified, conjunctivitis, ear pain, eye disorder, otitis media and refraction disorder.

Urogenital System

Abnormal kidney function, cystitis, dysuria, gynecomastia, prostatic disorder, unintended pregnancy, urinary frequency, urolithiasis and vaginal moniliasis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

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Take a Biofilm Approach To Infected Foot Wounds

BY MARK S. LESNEY
Senior Editor

WASHINGTON — Monotherapy may not be enough in the treatment of diabetic wound infections.

These infections are not caused by the planktonic or individual cellular form of mainly single-species bacteria proliferating in the wound, but rather are caused by a complex, multicell vegetative mixed-bacterial state known as a biofilm, which has to be treated as a unique and dangerous organism in its own right, if treatment is to prove effective, Dr. Randall Wolcott said at a meeting sponsored by George Washington University Hospital.

The medical biofilm concept of infection is a fairly new one, and a recent review noted that almost every bodily system is affected by a biofilm disease. He estimated that every year, more than 10 million people come down with biofilm diseases, from endocarditis to necrotizing fasciitis.

Many believe slough is merely some mixture of white blood cells, protein, and deteriorated host tissue, but it is actually part of a complex biofilm.

This translates to more than 500,000 people a year who die from a biofilm disease, and it is time practitioners realized that the infected diabetic foot wound is a biofilm disease as well, in order to treat it appropriately, said Dr. Wolcott of the department of microbiology and immunology at Texas Tech University, Lubbock, and the Southwest Regional Wound Care Center in that city.

He used the dramatic imagery from the science fiction movie "Terminator II," in which a killer police officer, made of liquid metal, is first shattered into pieces and yet quickly reassembles with equal destructive capability as before.

The behavior of biofilms is similar, he pointed out. Once bacteria attach to a wounded surface, "they form a microcolony. Once they reach a critical density, they start form-sensing, and they rise up above the surface and they start forming all these complex structures. One of those structures infests itself around the vasculature and they invade the host down through the vascular system. [They also] rise up over the surface for community defenses," he said.

This vegetative state behaves like a single organism "made of billions of billions of cells" including multiple bacterial species. A large portion of this "organism"—and he stressed treating it as such—includes gluey, sugar-protein matrices formed within the first 5 minutes of biofilm development. These protect the bacteria from harm by walling them off—not only from the host immune system, but also from many of the treatments that are used, Dr. Wolcott said.

Within 30 minutes, the biofilm is rising from the surface. It is controlled centrally by various intercellular communication molecules that act almost like hormones, and it reproduces by vegetative breaking and single-cell "seeds." The biofilm components summon white blood cells, with their phagocytic enzymes, which actually can provide nutrients for the biofilm; this explains much of the biochemistry we see, according to Dr. Wolcott.

The bacteria give up their individuality and live for the colony, with different regions producing different proteins, just as organisms have different brain cells, liver cells, and so on. One clinically important factor is that there are portions of the biofilm where the cells upregulate gene transfer to create phenotypic and genotypic diversity to survive. This includes the potential for transferring antibiotic resistance across species.

This understanding is very new, Dr. Wolcott said. "I just got a [2007] medical microbiology text and it does not mention biofilms," he noted, suggesting maybe that was why most of the audience might not have heard of these concepts.

However, practitioners did see biofilms in diabetic foot wounds every day without realizing it: the so-called slough that physicians routinely remove, or not, Dr. Wolcott added. Many believe slough is merely some mixture of white blood cells, protein, and deteriorated host tissue, but it is actually part of a complex biofilm—and one that will return exactly as before if even "one cell remains" still virulent, exactly as before without proper treatment.

"If I take off waxy biofilm … then I get waxy biofilm back. If I take off the fluffy biofilm I get the fluffy," he said. "So slough really is biofilm."

And if all these infections are really biofilms, then the next therapeutic step is to move from antibiotic monotherapies to include the use of antibiofilm agents and aggressive treatments, Dr. Wolcott said. This combined treatment is only in its infancy. It involves frequent, very aggressive debridement, coupled with biocide treatments that include heavy metal agents such as silver, gallium, and selenium. It is important to rotate treatments in order to prevent selective adaptation of the biofilm, which can happen not in weeks or months, but in days.

In his practice, he also thinks it critical to include the use of specific antibiofilm agents such as lactoferrin and xylitol, which are approved by the Food and Drug Administration for other purposes. He has even experimentally used predatory bacteriophages and various plant extracts known for their antibiofilm properties. Ultimately, "once you suppress the biofilm below a certain level … the wound starts contracting" and normal host healing can begin, he said.

Dr. Wolcott had no disclosures other than the use of materials that are not FDA approved for these indications. ■