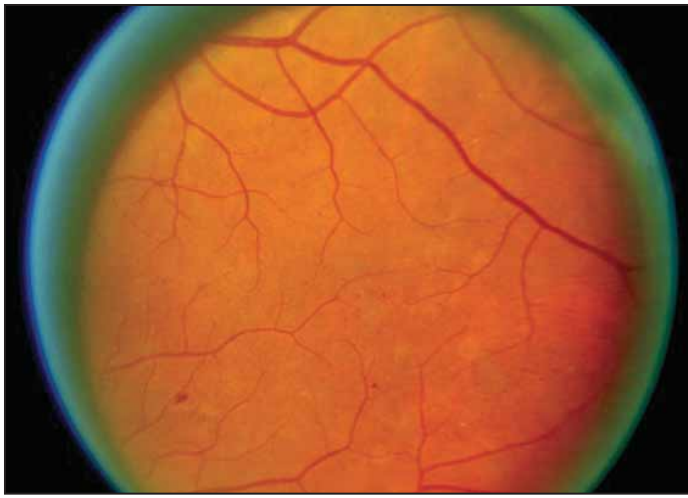


Mild nonproliferative diabetic retinopathy like this may be seen in patients who have impaired glucose tolerance but do not yet have diabetes, the study showed.



Retinopathy Found Prior To Diabetes Development

BY MIRIAM E. TUCKER
Senior Writer

SAN DIEGO — Diabetic retinopathy can occur in people who do not yet have diabetes, Richard Hamman, M.D., reported at the annual scientific sessions of the American Diabetes Association.

The incongruous finding, among patients with impaired glucose tolerance

(IGT) or impaired fasting glucose (IFG) who had participated in the Diabetes Prevention Program (DPP), suggests that the current cutoffs used to diagnose diabetes may need to be revised, said Dr. Hamman, professor and chair of the department of preventive medicine and biometrics at the University of Colorado, Denver.

More patients will need to be studied to determine whether the retinal lesions found in these "prediabetic" individuals represent early diabetic changes or perhaps are more indicative of arteriolar changes in people who are at risk for atherosclerotic vascular disease in general. Still, the finding does suggest that "a good retinal exam during the transition from prediabetes to early diabetes is important," Dr. Hamman said at a press briefing at the ADA meeting.

Little is known about exactly when retinopathy develops in patients with type 2 diabetes, because the diagnosis often lags years behind the actual onset of high blood sugar. The DPP, which followed 3,234 high-risk individuals at 6-month intervals, afforded a unique opportunity to date precisely the development of retinopathy in relation to diabetes onset, he noted.

At a mean of 5.5 years between randomization in DPP and the taking of retinal photos, retinopathy of any degree was found in 15% of the 301 who developed diabetes during the trial and in 10% of 585 who did not. Retinopathy of grade 20 or higher—considered more indicative of true diabetes-related changes—was found in 12.5% of those with diabetes of short duration and in 8% of those who remained as IGT or IFG.

Similarly, the proportions who had only microaneurysms were 11% and 7%, respectively. Moderate nonproliferative diabetic retinopathy was detected in 2% of those who did not meet the criteria for diabetes during the trial and in 1% of those who did, a nonsignificant difference that nonetheless follows the same trend.

These data also show that retinopathy may appear far earlier in the course of diabetes than was previously thought. "Just 6-12 months after diabetes onset, almost 13% had retinopathy," Dr. Hamman remarked at the press briefing.

Among the subjects who did not develop diabetes, triglycerides were the only other risk factor associated with the development of retinopathy, with no differences in other lipid parameters, hemoglobin A_{1c}, or blood pressure between those who developed retinopathy and those who did not.

But among those who developed diabetes, blood pressure and HbA_{1c} levels were associated with the presence of retinopathy. Prior to their diabetes diagnosis, those with retinopathy had a mean blood pressure of 129/80 mm Hg, compared with 124/78 mm Hg among those without retinopathy, a significant difference. After the diabetes diagnosis, those values were 127/79 mm Hg and 123/77 mm Hg, respectively.

The study is being funded by the National Institutes of Health and the Centers for Disease Control and Prevention. ■

ZOVIRAX® (acyclovir) Cream 5% Begins to Comfort on Contact to Heal Herpes Fast

- Targeted treatment begins to comfort at the site¹
- Significantly shortens lesion duration vs placebo*¹
- Significantly shortens pain duration vs placebo*¹

* Shorter duration of episode: in study 1, acyclovir (n=324) 4.3 days vs vehicle (n=346) 4.8 days (P=0.010). In study 2, acyclovir (n=328) 4.6 days vs vehicle (n=343) 5.2 days (P=0.007). Shorter duration of pain: in study 1, acyclovir (n=334) 2.9 days vs vehicle (n=352) 3.2 days (P=0.024). In study 2, acyclovir (n=348) 3.1 days vs vehicle (n=351) 3.5 days (P=0.027).

Reference: 1. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T, for The Acyclovir Cream Study Group. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother.* 2002;46:2238-2243.

ZOVIRAX® (acyclovir) Cream 5%

INDICATIONS AND USAGE

ZOVIRAX Cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

CONTRAINDICATIONS

ZOVIRAX Cream is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.

PRECAUTIONS

General: ZOVIRAX Cream is intended for cutaneous use only and should not be used in the eye or inside the mouth or nose. ZOVIRAX Cream should only be used on herpes labialis on the affected external aspects of the lips and face. Because no data are available, application to human mucous membranes is not recommended. ZOVIRAX Cream has a potential for irritation and contact sensitization (see ADVERSE REACTIONS). The effect of ZOVIRAX Cream has not been established in immunocompromised patients.

Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with ZOVIRAX Cream.

Carcinogenesis, Mutagenesis, Impairment or Fertility: Systemic exposure following topical administration of acyclovir is minimal. Dermal carcinogenicity studies were not conducted. Results from the studies of carcinogenesis, mutagenesis and fertility are not included in the full prescribing information for ZOVIRAX Cream due to the minimal exposures of acyclovir that result from dermal application. Information on these studies is available in the full prescribing information for ZOVIRAX Capsules, Tablets, and Suspension and ZOVIRAX for Injection.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects

or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Systemic acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topically applied acyclovir is excreted in breast milk. Systemic exposure following topical administration is minimal. After oral administration of ZOVIRAX, acyclovir concentrations have been documented in breast milk in 2 women and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Nursing mothers who have active herpetic lesions near or on the breast should avoid nursing.

Geriatric Use: Clinical studies of acyclovir cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic absorption of acyclovir after topical administration is minimal (see CLINICAL PHARMACOLOGY).

Pediatric Use: Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

ADVERSE REACTIONS

In 5 double-blind, placebo-controlled trials, 1,124 patients were treated with ZOVIRAX Cream and 1,161 with placebo (vehicle) cream. ZOVIRAX Cream was well tolerated; 5% of patients on ZOVIRAX Cream and 4% of patients on placebo reported local application site reactions.

The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each event occurred in less than 1% of patients receiving ZOVIRAX Cream and vehicle. Three patients on ZOVIRAX Cream and 1 patient on placebo discontinued treatment due to an adverse event.

An additional study, enrolling 22 healthy adults, was conducted to evaluate the dermal tolerance of ZOVIRAX Cream compared with vehicle using single occluded and semi-occluded patch testing methodology. Both ZOVIRAX Cream and vehicle showed a high and cumulative irritation potential. Another study, enrolling 251 healthy adults, was conducted to evaluate the contact sensitization potential of ZOVIRAX Cream using repeat insult patch testing methodology. Of 202 evaluable subjects, possible cutaneous sensitization reactions were observed in the same 4 (2%) subjects with both ZOVIRAX Cream and vehicle, and these reactions to both ZOVIRAX Cream and vehicle were confirmed in 3 subjects upon rechallenge. The sensitizing ingredient(s) has not been identified.

The safety profile in patients 12 to 17 years of age was similar to that observed in adults.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir cream. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to acyclovir cream.

General: Angioedema, anaphylaxis.

Skin: Contact dermatitis, eczema, application site reactions including signs and symptoms of inflammation.

OVERDOSAGE

Overdosage by topical application of ZOVIRAX Cream is unlikely because of minimal systemic exposure (see CLINICAL PHARMACOLOGY).

DOSAGE AND ADMINISTRATION

ZOVIRAX Cream should be applied 5 times per day for 4 days. Therapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear). For adolescents 12 years of age and older, the dosage is the same as in adults.

HOW SUPPLIED

Each gram of ZOVIRAX Cream 5% contains 50 mg acyclovir in an aqueous cream base. ZOVIRAX Cream is supplied as follows:
2-g tubes (NDC 64455-994-42).
5-g tubes (NDC 64455-994-45).

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

Manufactured by

GlaxoSmithKline
Research Triangle Park, NC 27709
for

BIOVAIL
Pharmaceuticals, Inc.

Bridgewater, NJ 08807

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Comfort Begins on Contact



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