

# Intrauterine Infection Linked to Cerebral Palsy

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RIVIERA MAYA, MEXICO — Prenatal exposure to intrauterine infection is emerging as a possible cause of many cases of cerebral palsy previously classified as idiopathic, Dr. Errol Norwitz said at a conference on obstetrics, gynecology, perinatal medicine, neonatology, and the law.

“Recent data suggest that it is the fetus’s inflammatory response which caus-

es problems both in terms of preterm labor and neuronal injury,” said Dr. Norwitz, director of maternal-fetal medicine at Yale–New Haven Hospital, Conn. “Even in the absence of a positive amniotic fluid culture in women with chorioamnionitis, we see proinflammatory cytokines, prostaglandins, and other markers of infection.”

Animal studies have demonstrated direct brain injury from such infections. Fetal rabbits exposed to intrauterine *Es-*

*cherichia coli* infections develop white matter injuries, while fetal rhesus monkeys demonstrated brain injuries associated with chronic group B streptococcus intrauterine infections.

In human fetuses, epidemiologic evidence points to a similar association, with infection and brain injury leading to cerebral palsy, Dr. Norwitz said. “In normal- and low-birth-weight infants, we see an association between periventricular leukomalacia and both group B strep sep-

sis and histologic chorioamnionitis.”

The premature labor associated with intrauterine infection appears to be triggered by the fetus’s inflammatory response, as a way to escape the contaminated intrauterine environment. “What we are suggesting here is that the infectious agent gets into the baby by the ascending route or, rarely, across the placenta, and the baby’s inflammatory response leads independently to preterm birth,” Dr. Norwitz said. “It’s a protective mechanism, because if the baby didn’t do this, it would probably die in utero due to overwhelming sepsis.”

The exact mechanism of neuronal damage remains unknown, he said. “There appears to be a fetal vasculitis with activation of leukocytes. This causes a huge surge in proinflammatory cytokines, with an imbalance between the proinflammatory and the anti-inflammatory cytokines. Some of the activated cells appear to cross the blood-brain barrier and cause damage to the brain.”

In fact, he said, some studies have shown that elevated proinflammatory cytokines are common in the brains of patients with cerebral palsy and periventricular leukomalacia. A 1997 study found tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , or interleukin-6 in 88% of cases with the lesions, but only 18% of cases without them (Am. J. Obstet. Gynecol. 1997;177:406-11). Another study of neonatal brains with and without the lesions concluded that an immune-mediated inflammatory process might play a role in the development of such lesions, with TNF- $\alpha$ , a myelinotoxic factor, perhaps playing the major role (Neurology 2001;56:1278-84).

Interestingly, higher levels have also been noted in the serum and amniotic fluid of neonates who later developed cerebral palsy (Ann. Neuro. 1999;44:665-75; Am. J. Obstet. Gynecol. 1997;117:19-26).

Given these findings, questions arise about a possible protective effect of immediate cesarean delivery in mothers with intrauterine infection, Dr. Norwitz said. “Right now, intrauterine infection is an absolute indication for delivery, but in some cases, it can take 18-36 hours to get these babies delivered. Are these kids, sitting in this infected environment for all that time, at increased risk? Once we make the diagnosis, should we be getting that baby out immediately by cesarean? Currently there is no indication for this, but I wouldn’t be surprised if this changes in 5-10 years, as our understanding of this area develops.”

Estimates are that only 10% of cerebral palsy cases are due to an identifiable intrapartum event, he said. But this statistic and the evolving understanding of the possible role of infection don’t ease the difficulty of defending such cases in court, cautioned John Scully, a defendant’s lawyer from Dallas. “The jury comes in with a preconceived notion that all CP is due to birth injury, and could have been avoided if a C-section was performed early enough. It’s very difficult to convince them that in 90% of the cases, the cause is simply not known.”

The conference was sponsored by Boston University. ■

## DIFFERIN® (adapalene) Cream, 0.1%

### Rx Only BRIEF SUMMARY

For topical use only. Not for ophthalmic, oral, or intravaginal use.

**INDICATIONS AND USAGE:** DIFFERIN® Cream is indicated for the topical treatment of acne vulgaris.

**CONTRAINDICATIONS:** DIFFERIN® Cream should not be administered to individuals who are hypersensitive to adapalene or any of the components in the cream vehicle.

**PRECAUTIONS: General:** If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of “waxing” as a depilatory method should be avoided on skin treated with adapalene.

**Information for Patients:** Patients using DIFFERIN® Cream should receive the following information and instructions:

1. This medication is to be used only as directed by the physician.
2. It is for external use only.
3. Avoid contact with the eyes, lips, angles of the nose, and mucous membranes.
4. Cleanse area with a mild or soapless cleanser before applying this medication.
5. Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.
6. Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis, and eye irritation.
7. This medication should not be applied to cuts, abrasions, eczematous or sunburned skin.
8. Wax epilation should not be performed on treated skin due to the potential for skin erosions.
9. During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of this medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Overall clinical benefit may be noticed after two weeks of therapy, but at least eight weeks are required to obtain consistent beneficial effects.

**Drug Interactions:** As DIFFERIN® Cream has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime rind) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN® Cream. If these preparations have been used, it is advisable not to start therapy with DIFFERIN® Cream until the effects of such preparations in the skin have subsided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day, and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day. These doses are up to 8 times (mice) and 6 times (rats) in terms of mg/m<sup>2</sup>/day the maximum potential exposure at the recommended topical human dose (MRHD), assumed to be 2.5 grams DIFFERIN® Cream, which is approximately 1.5 mg/m<sup>2</sup> adapalene. In the oral study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats was observed. No photocarcinogenicity studies were conducted. Animal studies have shown an increased risk of skin neoplasms with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vivo* (mouse micronucleus test) and *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) studies.

Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day (up to 80 times the MRHD based on mg/m<sup>2</sup> comparisons). No effects of adapalene were found on the reproductive performance or fertility of the F<sub>1</sub> males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F<sub>2</sub> generation.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN® Cream is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 12 have not been established.

**ADVERSE REACTIONS:** In controlled clinical trials, local cutaneous irritation was monitored in 285 acne patients who used DIFFERIN® Cream once daily for 12 weeks. The frequency and severity of erythema, scaling, dryness, pruritus and burning were assessed during these studies. The incidence of local cutaneous irritation with DIFFERIN® Cream from the controlled clinical studies is provided in the following table:

Incidence of Local Cutaneous Irritation with DIFFERIN® Cream from Controlled Clinical Studies (N=285)				
	None	Mild	Moderate	Severe
Erythema	52% (148)	38% (108)	10% (28)	<1% (1)
Scaling	58% (166)	35% (100)	6% (18)	<1% (1)
Dryness	48% (136)	42% (121)	9% (26)	<1% (2)
Pruritus (persistent)	74% (211)	21% (61)	4% (12)	<1% (1)
Burning/Stinging (persistent)	71% (202)	24% (69)	4% (12)	<1% (2)

Other reported local cutaneous adverse events in patients who used DIFFERIN® Cream once daily included: sunburn (2%), skin discomfort-burning and stinging (1%) and skin irritation (1%). Events occurring in less than 1% of patients treated with DIFFERIN® Cream included: acne flare, dermatitis and contact dermatitis, eyelid edema, conjunctivitis, erythema, pruritus, skin discoloration, rash, and eczema.

**OVERDOSAGE:** DIFFERIN® Cream is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, scaling, or skin discomfort may occur. The acute oral toxicity of DIFFERIN® Cream in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

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## DIFFERIN® (adapalene gel) Gel, 0.1%

### Rx Only BRIEF SUMMARY

INDICATIONS AND USAGE: DIFFERIN® Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: DIFFERIN® Gel should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle gel.

WARNINGS: Use of DIFFERIN® Gel should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

PRECAUTIONS: General: If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

**Drug Interactions:** As DIFFERIN® Gel has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN® Gel. If these preparations have been used, it is advisable not to start therapy with DIFFERIN® Gel until the effects of such preparations in the skin have subsided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

In a series of *in vivo* and *in vitro* studies, adapalene did not exhibit mutagenic or genotoxic activities.

**Pregnancy:** Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN® Gel is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 12 have not been established.

**ADVERSE REACTIONS:** Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN® Gel during clinical trials were reversible upon discontinuation of therapy.

**OVERDOSAGE:** DIFFERIN® Gel is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of DIFFERIN® Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

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