© 2003 Wiley-Liss, Inc.

Correspondence

MALE PERICONCEPTIONAL RIBAVIRIN-INTERFERON ALPHA-2B EXPOSURE WITH NO ADVERSE FETAL EFFECTS

To the Editor:

Ribavirin (1-beta-D-Ribofuranosyl-1,2,4-triazole-3-carboximide) is an antiviral agent, indicated in the treatment of severe infections. It is administered orally, intravenously, or by aerosol inhalation. Ribavirin and recombinant interferon alpha-2b combination therapy is now widely recommended for the treatment of chronic hepatitis C.

We report a case of a paternal periconceptional exposure to ribavirin and recombinant interferon alpha-2b therapy. Our patient affected by chronic hepatitis C received interferon alpha-2b (3 mU three times a week) and ribavirin (1,000 mg daily). He started therapy 4 weeks before the last menstrual cycle of her wife and continued after the pregnancy was discovered. The couple decided to continue the pregnancy after counseling. No evidence for fetal malformations was found by prenatal ultrasound. The male infant, born at term, had no dysmorphic features or malformations. His head circumference was 36 cm (50th centile), his length was 50 cm (50–75th centile), and birth weight was 3,380 g (50th–75th centile) (Tanner and Whitehouse, 1976).

To our knowledge, only two cases of paternal exposure at the time of conception have been reported and these were healthy newborns (Hagenbarth et al., 2001). Reliable data on the teratogenic and mutagenic risks of ribavirin and recombinant interferon alpha-2b therapy in humans are lacking. It has been difficult to determine whether this male exposure is teratogenic.

ANIMAL STUDIES

Ribavirin has been found to be mutagenic, teratogenic, and/or embryo-lethal in several species of animals (Johnson, 1990). A rigorous method to establish the developmental toxicity of drugs is the FDA Segment II protocol (Collins, 1978) with both rats and rabbits that have been tested with the following results. In rats, 1 mg/kg/day oral dose of ribavirin given on gestational days 6–15 produced no effects, whereas a 10 mg/kg/day dose resulted in teratogenicity. In rabbits, 1 mg/kg/day oral dose given on gestational days 6–18 produced fetal resorptions; the lower doses of 0.1 or 0.3 mg/kg/day had no detrimental effects. Intraperitoneal administration of ribavirin during gestation induced malformations of the craniofacial and limb bones of mice (Kochhar et al., 1980). Ribavirin, administered by oral, intraperitoneal, or intravenous routes, was associated in hamsters, with defects of the limbs, eyes, and brain (Kilham and Ferm, 1977; Ferm et al., 1978) and in rats with defects of the brain, eyes (Ferm et al., 1978), and sperm shape (Narayana et al., 2002). In both rats and hamsters, oral administration of the drug seemed to be more teratogenic by other routes, suggesting that metabolism of ribavirin in the maternal gastrointestinal tract and/or liver may change it into its active form (Ferm et al., 1978).

Recombinant interferon alpha-2b, administered orally or intramuscularly, has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60 kg adult).

HUMAN STUDIES: EXPOSED FEMALES

Because of frequent association of ribavirin exposure with adverse effects on pregnancy in animal experiments, the marketing approval of ribavirin specified that it be avoided in women or girls who are pregnant or may become pregnant for at least 6 months after therapy (Anonymous, 1986). No epidemiological studies of congenital anomalies among infants born to women treated with ribavirin during pregnancy have been reported. Moreover, no adverse effects were reported by Atmar et al. (1992), where nine children of ribavirin-treated women for severe measles during the second half of pregnancy did not have an increased incidence of anomalies. Because ribavirin is administered as an aerosol, concern has been expressed regarding the possible exposure of hospital staff to this drug while it is administered to infants (Bortolussi and Gold, 1988), but a study of 19 nonpregnant nurses who were caring for infants being treated with ribavirin did not reveal measurable levels of ribavirin in blood or urine (Rodriguez et al., 1987). Based on these findings, it was concluded that ribavirin administration is apparently safe for hospital personnel (Bortolussi and Gold, 1988).

Interferons may impair human fertility and evidence provided for recombinant interferon alpha-2b and ribavirin when administered alone indicates that both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents. No reproductive toxicology studies have been performed using recombinant interferon alpha-2b in combination with ribavirin.

HUMAN STUDIES: EXPOSED MALES

Ribavirin is known to accumulate in intracellular components, from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect on fertilization of the ova. Neither experimental nor clinical evidence for birth defects after paternal exposure to ribavirin exists and because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners. For the evidence gathered, special precautions are recommended by the manufacturer as follows: male patients taking riba-

*Correspondence to: Sebastiano Bianca, Registro Siciliano Malformazioni Congenite, Genetica Medica, Dipartimento di Pediatria, Via S. Sofia, 78, 95123, Catania, Italy. E-mail: sebastiano.bianca@tiscalinet.it
Received 14 February 2002; Accepted 22 July 2002
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.10105

virin and their partners must practice effective contraception during and up to 7 months after intake of ribavirin, and men taking ribavirin whose partners are pregnant must be advised to use condom to minimize delivery of ribavirin to the vagina (Hagenbarth et al., 2001).

Ribavirin is listed as a category X and interferon as a category C drug by the Food and Drug Administration with regards to pregnancy risk, but the accuracy of this type of classification has been questioned (Friedman et al., 1990; Addis et al., 2000). We think that this classification is only a basis for counseling a couple with an at-risk pregnancy and that the teratogenic counseling should include also the evaluation of animal and human studies available. The use of drugs with a potential teratogenic effect needs careful counseling and education of both prescribers and patients.To our knowledge, no case control study on ribavirin-interferon alpha 2b exposure has been carried out. Therefore, individual case reports, such as this, are important to evaluate the safety of this therapy.

We agree with other researchers (Hagenbarth et al., 2001; Mishkin and Deschenes, 2001) that it is necessary to encourage continuation of pregnancy in the event of either paternal or maternal preconceptional exposure to ribavirin-interferon alpha-2b therapy.

Sebastiano Bianca*
Registro Siciliano Malformazioni Congenite
Genetica Medica
Dipartimento di Pediatria
Università di Catania
Catania, Italy

Giuseppe Ettore
Registro Siciliano Malformazioni Congenite
Divisione di Ostetricia e Ginecologia
Az. Ospedaliera "Garibaldi"
Catania, Italy

LITERATURE CITED

Addis A, Sharabi S, Bonati M. 2000. Risk classification systems for drug use during pregnancy: are they a reliable source of information? Drug Saf 23:245–253.

Anonymous. 1986. Ribavirin aerosol approved for severe cases of RSV in infants and young children. FDA Drug Bull 16:7.

Atmar RL, Englund JA, Hammill H. 1992. Complications of measles during pregnancy. Clin Infect Dis 14:217–226.

Bortolussi RA, Gold R. 1988. Ribavirin aerosol therapy: safety for staff. CMAJ 138:204.

Collins TFX. 1978. Reproduction and teratology guidelines: review of deliberations by the National Toxicology Advisory Committee's reproduction panel. J Environ Pathol Toxicol 2:141–147.

Ferm VH, Willhite C, Kilham L. 1978. Teratogenic effects of ribavirin on hamster and rat embryos. Teratology 17:93–102.

Friedman JM, Little BB, Brent RL, Cordero JF, Hanson JW, Shepard TH. 1990. Potential human teratogenicity of frequently prescribed drugs. Obstet Gynecol 75:594–599.

Hagenbarth K, Maurer U, Kroisel PM, Fickert P, Trauner M, Stauber RE. 2001. No evidence for mutagenic effects of ribavirin: report of two normal pregnancies. Am J Gastoenterol 96:2286–2287.

Johnson EM. 1990. The effects of ribavirin on development and reproduction: a critical review of published and unpublished studies in experimental animals. J Am Coll Toxicol 9:551–561.

Kilham L, Ferm VH. 1977. Congenital anomalies induced in hamster embryos with ribavirin. Science 195:413–414.

Kochhar DM, Penner JD, Knudsen TB. 1980. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. Toxicol Appl Pharmacol 52:99–112.

Mishkin D, Deschenes M. 2001. Conception soon after discontinuing interferon/ribavirin therapy: a succesful outcome. Am J Gastoenterol 96: 2285.

Narayana K, D'Souza UJ, Seetharama Rao KP. 2002. Ribavirin-induced sperm shape abnormalities in Wistar rat. Mutat Res 15:193–196.

Rodriguez WJ, Bui RH, Connor JD, Kim HW, Brandt CD, Parrott RH, Burch B, Mace J. 1987. Environmental exposure of primary care personnel to ribavirin aerosol when supervising treatment of infants with respiratory syncytial virus infection. Antimicrob Agents Chemother 31:1143–1146.

Tanner JM, Whitehouse RH. 1976. Clinical longitudinal standards for height, weight, height velocity, weight velocity and stages of puberty. Arch Dis Child 51:170–179.