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REPORT

Is Ribavirin Toxic?

Since the publication of this article, the FDA has approved Ribavirin for Hepatitis C, but on the condition that the patient has first failed to benefit from interferon.

Ribavirin can be bought over the counter in many countries and has been used safely by millions of people for more than 10 years. The FDA insists, however, that ribavirin is a dangerous drug that should only be used under the supervision of a physician.

The Life Extension Foundation disputes the FDA's assertions that ribavirin is a dangerous drug. One reason is that the author of this article has personally consumed enough ribavirin since 1983 to be dead, according to what the FDA says. Foundation members have used ribavirin since 1983 to suppress acute and chronic viral infections, and there has yet to be one report of the toxicity problems the FDA warns about.

It could be that vitamin supplement users are protected against the anemia that the FDA alleges ribavirin has the potential to cause in some people. Published studies show that folic acid and vitamin B12 are especially effective in treating anemia and that the hormone melatonin can protect against chemotherapy-induced anemia. It might be a good idea for those taking ribavirin to also take at least 500 micrograms of melatonin at night, in addition to the daily intake of folic acid and vitamin B12.

What makes the Foundation especially skeptical of the FDA's assertions of toxicity are the many published studies showing that ribavirin is a relatively safe drug. The historical political bias the FDA has shown against ribavirin also brings the agency's objectivity into question.

The FDA's toxicity warnings are based partly on a recent six-month hepatitis trial showing that 10 percent of participants developed anemia. The concern is that anemia can be a serious problem for those with severe coronary artery disease or pre-existing blood diseases. The FDA wants all of those taking ribavirin to have their blood tested first, and again at two week intervals thereafter. The Foundation does not disagree with this precaution; in fact, it encourages regular blood testing.

The problem is, in the real world when someone is developing acute viral symptoms, it is often impossible to have blood tests done right away. That is one reason why it is so important to have an annual blood test to find out if you are anemic in the first place. In the 10 percent of ribavirin users who developed anemia in this study, the condition disappeared shortly after cessation of ribavirin therapy, which was resumed when blood cell counts return to normal levels.

Pregnant women or those who may become pregnant should avoid ribavirin. This is a good precaution for any anti-viral drug, but not all studies show ribavirin to be a problem. The FDA lists a wide range of potentially lethal side effects for long-term use of ribavirin and interferon in combination to treat hepatitis C, but most of these side effects are caused by interferon, not ribavirin. The FDA is mandating that hepatitis C patients first fail a brutal six month regimen of interferon alone, before being allowed to try ribavirin, even though it is interferon that is more toxic.

Most people who use ribavirin by itself to knock out common flu viruses, or to treat lethal infections such as viral cardiomyopathy, Hantavirus, viral encephalitis or influenza, do so for short periods (two to 10 days), taking 600 to 1,200 milligrams per day. There are more than 2,000 published studies that discuss ribavirin, and only 261 of these studies mention any toxicity problems.

On the following pages are summaries of what is in the scientific literature concerning ribavirin and toxicity:

- "Long-term therapy in humans using combination ribavirin and interferon to treat hepatitis C enhances the therapeutic efficacy two to threefold without increasing the toxicity." *Scandinavian Journal of Gastroenterology*, Supplement (Norway), 1997, 32/223 (46-49)
- "Treatment of measles patients with ribavirin resulted in shorter and less-severe disease, as well as fewer complications, compared with patients in the placebo group. Ribavirin was well tolerated. There were no side effects or changes in laboratory

values that could be associated with drug-related toxicity." *Clinical. Therapeutics (USA)* , 1981, 3/5 (389-396)

- "Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. A meta-analysis of individual patient data from European centers shows that the sustained response rate was significantly higher for interferon-ribavirin combination therapy than for interferon or ribavirin monotherapy. No serious adverse events were observed. The efficacy of interferon-ribavirin therapy appears to be enhanced two to threefold over interferon monotherapy in all major subgroups of chronic hepatitis C patients tested. In view of its acceptable toxicity profile, interferon-ribavirin combination therapy is a candidate for the new standard therapy for chronic hepatitis C." *Journal of Hepatology (Denmark)*, 1997, 26/5 (961-966)
(The FDA wants hepatitis C patients to first fail interferon therapy before being allowed to use ribavirin and interferon, despite the above three studies showing little or no toxicity for the combination of these two drugs.)
- "The efficacy and toxicity of ribavirin (and another anti-viral drug called didanosine, or ddl) given for six weeks were investigated in the mouse form of acquired immunodeficiency syndrome model. The results showed a significant protection against splenomegaly, lymphadenopathy and hypergammaglobulinemia in mice treated with ribavirin by itself at a human equivalent dose of 1,800 mg per day. Ribavirin (and the other antiviral drug) protected against the loss of T cells in spleen and restored the capacity of splenocytes to proliferate after activation with a mitogenic agent. Moreover, the drug combination resulted in a protection of the spleen and cervical lymph node architectures and a regression of germinal centers. Toxicity to the blood appeared at a human equivalent dose of 9,000 mg per day of ribavirin." *Journal of Pharmacology and Experimental Therapeutics (USA)*, 1996, 279/2 (1009-1017)
(This study shows that seven to 14 times more ribavirin than that administered to humans produces blood cell toxicity in mice. Humans usually take 600 to 1,200 mg a day of ribavirin.)
- "Ribavirin protects mice against the effects resulting from retrovirus infection at doses of less than or equal to the human equivalent dose of 3,600 mg a day, but induces severe blood cell toxicity at doses less than or equal to the human equivalent dose of 7,200 mg a day." *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (USA)*, 1996, 12/5 (451-461)
(Hepatitis C patients only need 1,200 mg a day of ribavirin.)
- "The effects of testicular toxicity of ribavirin and its reversibility in mice were evaluated. At the human equivalent dose of 2,520 mg a day, there was mild testicular damage after six months. At the human equivalent dose of 5,400 to 10,800 mg a day, there was significant testicular damage after six months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within one to two spermatogenesis cycles, which was consistent with negligible effects." *Toxic Substances Journal. (USA)*, 1994, 13/3 (171-186)
The FDA uses this study to support its position that most hepatitis C patients should not receive 1,200 mg a day of ribavirin.)
- A troubling study showed that the administration of the human equivalent dose of as little as 792 mg of ribavirin for only 10 days to cats resulted in uniform significant toxicities throughout their bodies. *Reported in Journal of Veterinary. Pharmacology and Therapeutic, (United Kingdom)*, 1993, 16/3 (301-316).
(We question the validity of this study because: 1) None of the cats treated with higher doses of ribavirin for feline leukemia in the Life Extension Foundation laboratory ever experienced this type of toxicity; 2) If ribavirin is as toxic as this study indicates, it would have never been approved by any health ministry, including the FDA; and 3) If ribavirin is as toxic as is indicated in this study, you would not be reading this article because its author would be dead.
- "To evaluate the efficacy of oral ribavirin, 24 patients with chronic active hepatitis B were put on a course of treatment with 800 to 1,000 mg per day of ribavirin and/or interferon. Ribavirin, alone and in combination with interferon-beta, decreased hepatitis B virus levels in most patients to approximately half of baseline levels. Interferon alone exerted the most inhibitory effect on hepatitis B virus activity. Ribavirin was well tolerated, but the dose was transiently reduced in two cases because of mild anemia, although all patients completed the treatment schedule. The combination of interferon and ribavirin did not appear to result in greater toxicity. These results indicate that ribavirin suppresses hepatitis B virus replication, although its effect is less than that of interferon, and that it may be useful as adjunctive therapy for chronic hepatitis B." *Hepatology (USA)*, 1993, 18/2 (258-263)
- "When developmental toxicity of ribavirin was examined, few if any, developmental malformations were present that could be related with confidence to the drug. Several malformed fetuses were present in the highest dose level tested in rats (a human equivalent of only 720 mg a day) from days 6 to 15 of pregnancy. When evaluated for effects on reproduction and postnatal survival in rats, ribavirin at human equivalent doses of 4,320 to 6,480 mg per day produced statistically significantly and/or clearly dose-related increased incidences of fetal resorptions, abnormalities, and reduced postnatal survival. Most significantly, pregnant baboons (most similar to humans) given ribavirin orally at human equivalency levels of 4,320 mg to 8,640 mg per day during critical periods of differentiation and organogenesis were reported to have produced no adverse effects on in utero development." *Journal of the American College of Toxicology (USA)*, 1990, 9/5 (551-561)
(Women should avoid anti-viral drugs, based upon studies showing potential risk. The FDA says that ribavirin has produced embryonic damage in all "adequate" studies, but clearly there are studies showing that ribavirin does not always produce teratogenic [creating abnormalities in the embryos and fetuses] effects.)
- "Ribavirin was tested to determine its effects on the offspring of male rats. Human equivalent doses of 3,600 to 14,400 mg per day were administered for five days. Ribavirin was regarded as being devoid of any mutagenic potential demonstrable by a rat dominant lethal assay." *Mutation Research. (Netherlands)*, 1987, 188/1 (29-34)
(Despite this positive study, males and females attempting impregnation, as well as females who are already pregnant should avoid anti-viral drugs like ribavirin.)
- "Nine of 10 patients with AIDS had a CD4 count of less than 100 and all patients with the AIDS-related complex had a CD4 count of less than 200. Oral ribavirin was administered in the high dose of 1,200 mg twice daily for 3 days followed by 600 mg

per day for up to one year. Ribavirin treatment was well tolerated, with anemia requiring transfusion in one of the 10 patients with AIDS receiving the drug for 8 weeks; no other significant toxicity occurred. Six of nine patients initially positive for HIV-1 in the blood became negative during ribavirin treatment. Six of nine patients with AIDS had a twofold improvement in lymphoproliferative response with ribavirin treatment. The conclusions were that 600 mg a day of ribavirin was well tolerated and safe in the patients with severe AIDS and the AIDS-related complex." *Annals Internal Medicine* (USA), 1987, 107/5 (664-674)
(*HIV infection itself can induce anemia, so it is not surprising that 10 percent of patients required a transfusion. There are now more effective drugs approved by the FDA to treat HIV than ribavirin.*)

Based on a review of the published studies about ribavirin toxicity, it is clear that the FDA is exaggerating the potential adverse side effects of ribavirin, and is denying this drug to hepatitis C victims for reasons that are not scientifically based.

How to Use Ribavirin

Next time you come down with the flu, instead of asking your doctor to prescribe antibiotics that have no effect against viruses, ask for a prescription for ribavirin capsules. Most people find that 200 mg of ribavirin, taken four to six times throughout the day, eradicates flu symptoms fast.

You might also ask your doctor for a subcutaneous injection of interferon-alpha (1.5 million units). The FDA has approved interferon-alpha to treat a wide variety of viral infections and certain cancers. Because high doses of interferon-alpha are toxic, most doctors are afraid to prescribe even a single moderate dose in order to help someone overcome the miseries of a chronic flu infection.

Ribavirin is not a scheduled drug. That means a doctor can legally prescribe it for any purpose, even though the FDA only allows the manufacturer to promote ribavirin to treat hepatitis C infections that have not responded to standard interferon therapy (3 million units administered subcutaneously three times a week for six months).

There are viruses that infect the heart and cause lethal viral-induced cardiomyopathy. Other viruses infect the brain and cause lethal viral-induced encephalitis. Influenza viruses infecting the lungs and upper respiratory tract are the most common form of acute viral infection that kills people fast. With ribavirin, there is now a proven drug available to Americans to treat these acute viral infections, but because the FDA restricts its promotion, only well informed people (such as Life Extension Foundation members) will have the knowledge to demand that a doctor prescribe ribavirin and also inform the doctor about dosage and contraindications.

Ribavirin has shown efficacy at doses as low as 600 mg a day. If a life-threatening viral infection is present, most doctors will prescribe 800 to 1,200 mg of ribavirin a day, in three to four divided doses until the symptoms subside. Anyone using ribavirin for more than seven days should have a blood test to make sure ribavirin is not causing anemia. The FDA says that a blood test should be done before ribavirin is taken just in case an anemic condition is present.

The FDA also recommends that those taking ribavirin have blood tests done at week two and four to make sure the drug is not causing anemia. The Life Extension Foundation suggests that those taking ribavirin also take 800 micrograms of folic acid three times a day along with at least 1,000 micrograms of vitamin B12 every day. Melatonin in doses ranging from 500 micrograms to 10 mg at bedtime also may reduce the risk of ribavirin-induced anemia and help to boost immune function.

If you already suffer from anemia, it is unwise to use ribavirin.

It is worth repeating that pregnant and lactating women are advised to avoid ribavirin, as well as women who are seeking to become pregnant, and men who are seeking to impregnate women. If you suffer from severe coronary heart disease or severe pulmonary disease such as emphysema, the FDA is concerned that acute anemia could occur in response to taking ribavirin, and that this anemia could cause those already suffering from an oxygen deficiency to encounter severe health problems. The FDA also cautions against using ribavirin if you have many other diseases including kidney disorders.

For those without a physician who will prescribe ribavirin, it may be wise to keep 50 to 100 200-mg ribavirin capsules in the medicine cabinet. Ribavirin can be purchased from Mexican pharmacies and imported for personal use. Lower-priced ribavirin is available by mail order from offshore companies. For a free directory of offshore companies that will ship ribavirin to Americans for personal use, write to: International Society for Free Choice, 9 Dubnoc Street, 64368, Tel Aviv, Israel.

Ribavirin has been defined as a "broad-spectrum anti-viral agent" in the scientific literature. It works by inhibiting viral replication, and most strains of flu virus disappear within 24 to 48 hours after initiating ribavirin therapy.

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