Conflict of interest

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References


DHEA and progesterone have a protective effect on ribavirin-induced hemolysis

To the Editor:

We read with great interest the recent article by Scherzer et al. who investigated the relationship between ITPA polymorphism and decreased hemoglobin levels in 308 Austrian patients [1]. In their cohort, they confirmed the protective effect of ITPA polymorphisms on ribavirin-induced anemia. However, surprisingly, premenopausal females in their population were less likely to develop ribavirin-induced anemia irrespective of the protective effect of ITPA mutations. In multivariate analysis of a >3 g/dl decrease in hemoglobin, menopause was the most significant variable (OR = 2.814, 95% CI 1.027–7.714, p = 0.044). A similar result was not observed when comparing men less than 50 and older than 50. Scherzer et al. tried to advance explanations for these differences between premenopausal and postmenopausal women related to the protective effect of female hormones.

We have recently developed a new in vitro tool for analysis of ribavirin-induced red blood cell lysis based on the ribavirin concentration [2]. This test can be used to study molecules able to inhibit ribavirin-induced hemolysis. We therefore used this test to evaluate molecules associated with a physiological decrease in plasma concentrations between premenopausal and postmenopausal women. We tested the following molecules in the presence of 2 mM ribavirin: β-estradiol, estradiol, estrone, progesterone, androstenedione, and DHEA. Under our experimental conditions, in the presence of 2 mM ribavirin (intraerythrocytic ribavirin concentration in treated patients [3]), a hemolysis rate of about 20% was obtained. The percentage hemolysis for this condition was set to 100%. Interestingly, progesterone and DHEA strongly and dose-dependently attenuated ribavirin-induced hemolysis (Fig. 1). The various experimental conditions were repeated 6 times. For example, by adding DHEA at concentrations of 0.01 mg/ml and 0.02 mg/ml to the ribavirin medium, hemolysis was decreased by 31.87% (±2.9%, p <0.001) and 63.93% (±0.96%, p <0.001), respectively. Addition of progesterone at a concentration of 100 μM decreased hemolysis by 39.17% (±2.75%, p <0.001). On the basis of our preliminary results, we also tested structural analogs of progesterone (mifepristone, levonorgestrel, and prednisone), which also demonstrated protection towards ribavirin-induced hemolysis but to a lesser extent (data not shown).

Plasma DHEA levels decrease progressively with age in both men and women with a marked disparity of concentrations observed in the same age-group [4]. Plasma DHEA levels are in the range 600 to 3400 ng/ml in women between the ages of 25 and 44 years, and in the range 120 to 2500 ng/ml in women between the ages of 45 and 75 years. The results presented in Fig. 1 show that a small variation in the DHEA concentration (from 0.01 mg/ml to 0.02 mg/ml) leads to a significant reduction of ribavirin-induced hemolysis. Circulating progesterone levels fall to below 1 ng/ml in postmenopausal women.

These results may provide an explanation for the data obtained by Scherzer et al. [1]. However, the way in which these molecules counteract the adverse effects of ribavirin on red blood cells remain unknown. It is commonly accepted that ribavirin-induced hemolysis is the result of a marked decrease in ATP levels in red blood cells, increasing susceptibility to oxidation [5]. However, only limited evidence is available concerning how ribavirin disrupts ATP homeostasis in red blood cells. Several hypotheses can be proposed, such as consumption of ATP for ribavirin phosphorylation of derivatized triphosphate. Another explanation could be enzyme inhibition of the salvage pathway of purine nucleotide synthesis in red blood cells. The protective effect of DHEA and progesterone on ribavirin-induced hemolysis could possibly be involved in the regulation of red blood cell ATP metabolism. The addition of...
of protease inhibitors, boceprevir or telaprevir, to peginterferon + ribavirin increases the frequency as well as the severity of anemia [6]. According to our results, DHEA and/or progesterone supplementation could be tested in patients treated for chronic hepatitis C, especially in the elderly to achieve serum concentrations similar to those of women in their 20s [7].

Finally, it could be interesting to quantify plasma DHEA and progesterone levels in patients treated for chronic hepatitis C. The concomitant decrease of these two hormones could corroborate the data reported by Scherzer et al. concerning the difference in sensitivity to ribavirin-induced hemolysis in postmenopausal women and women of reproductive age.

Conflict of interest

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References


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Reply to: “DHEA and progesterone have a protective effect on ribavirin-induced hemolysis”

To the Editor:
We like to thank Dr. Etienne Brochot and colleagues [1] for their comment on our paper [2] on the impact of gender on ribavirin induced anemia. Indeed, this result was unexpected. Dr. Brochot’s data support our findings by showing that progesterone and DHEA inhibit ribavirin induced hemolysis in vitro. We were also prompted to further explore this issue. We investigated the changes in parameters of erythropoiesis (hemoglobin, erythropoietin, reticulocyte count), iron status (ferritin, hepcidin), and sexual hormones (estrogen, progesterone, FSH, LH) in each 10 healthy women (age: 31.2 ± 6.2) with or without hormonal contraception (ethinyl estradiol + various gestagens) during one...