Retinoic acid activity on mammalian embryo in organ culture and evaluation of hazard and risk in correlation studies between molecular descriptors and ADME parameters in a series of X-category drugs

**INTRODUCTION**

The active derivative of vitamin A, retinoic acid (RA), as an essential component of cell-cell signaling during vertebrate organogenesis is important for normal embryonic development. RA is an endogenous agonist for retinoic acid receptors (RARs), the type II of nuclear receptors (RARα, RARβ, and RARγ) which are ligand-controlled transcription factors that function as heterodimers with retinoid X receptors (RXRs) to regulate cell growth, differentiation, survival and death. The concentration of RA must be within a very narrow range in order to avoid both deficiency and toxicity because the adding of vitamin A or RA to embryos can easily induce teratogenic effects including major alterations in organogenesis. (1-3) The results of many previous studies indicate that all endogenous retinoids (retinol, retinal, RA) are toxic and in some cases teratogenic (4, 5), therefore they are listed in the FDA Pregnancy category X drugs among a very diverse group of drugs with different structural features, mechanisms of action and clinical indications. (6) The influence of RA on development of embryonic teratoma was also a subject of our previous in vitro investigations (7, 8). In addition, in this study we explored molecular features of selected pregnancy category X drugs, including retino, retinal and retinoid acid, by correlation studies between computed molecular descriptors (MDs), predicted drug-likeness scores (dls) and ADME properties.

**METHODS**

**A) Teratoma development**

**RESULTS AND CONCLUSIONS**

- Mammalian embryo-derived teratoma investigation in organ culture (Fig. 1) treated with either retinoic acid (RA, c = 10⁻⁶ mol/L) or neural growth factor (NGF, 100 ng/mL) showed no influence on neural tissue differentiation.
- The combination of RA (c = 10⁻⁵ mol/L) and NGF (100 ng/mL) influenced the neural tissue differentiation (100%) and the total inhibition of epidermis, gland epithelium and cartilage (Table 1).
- The same effects were observed in experiments of teratoma development treated with RA alone in concentration, c = 10⁻⁶ mol/L.
- The results in this in vitro model revealed the potential teratogenicity of RA in higher concentrations (c = 10⁻⁵ mol/L) or in combination with NGF.
- Computed MDs and ADME parameters are listed in Table 2.
- Drug-likeness scores (dls) analysis revealed that 73% of investigated molecules with positive dls retinoid X Out of total, 45.9% of molecules were with dls = 0.5 - 1.7, 26% of dls = 0.3 - 0.5 and 18% of dls = 0.1 - 0.3 were also computed.
- Linear correlations were obtained between MD and dls (Fig. 3), also between molecular polarizability and molecular refractivity (Fig. 4). Insignificant collinearity were obtained with NRI dls v.s. Micap and pi energy. However, NRI dls found to increase with increasing of Micap and decreasing of pi energy (Fig. 5).
- In correlations of Micap and TPSA with TDX HERG, a two sets of molecules were obtained small alignment with high collinear relationship between TDX HERG either with Micap or TPSA (Fig. 8), while the other set represents a cluster of diverse molecules including retinoids. It was also found the exponential decrease of TDX HERG with the NRI dls decreasing (Fig. 9).
- For all retinoids (1-5) included in this study the predicted ADMET Risk was 4, CYP Risk 0 and TDI Risk 2, while TDI AFB1 Risk of 5 were predicted for retinol (8) and etretinate (4) (Table 2, Fig. 10).
- Pregnancy category X drugs have a potential not only for Zaganogran but also for other AEDs, therefore their prescription and the use in treatment of patients should be with extreme caution.

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