IN VITRO MODELS OF HEMATOPOIESIS: APPLICATION TO A CASE OF DRUG-INDUCED HEMATOTOXICITY.

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As part of the early preclinical development of a new antipsychotic compound, an unexpected red cell hypoplasia (i.e., reticulocytopenia, red marrow hypoplasia with increased M:E ratio) was detected in the rat dosed orally for up to 7 days. An erythropoeitin-mediated pathogenesis for this adverse effect was excluded after a mechanistic experiment. The effect of the drug on the formation of late erythroid and granulocyte-macrophage colony-forming units (CFU-E and CFU-GM) was quantitatively measured *in vitro* after direct exposure to the agent. In 2 successive assays, rat (from the femur of 2 animals) or human (from the iliac crest of one healthy donor) marrow cells were incubated (37°C, 5% CO_2) with the drug dissolved in the collection medium at final concentrations of 0, 3.10^{-7}, 10^{-6}, 3.10^{-6},10^{-5} and 3.10^{-5} M. In the presence of adequate growth factors, CFU-E were cultured for 48 hr (rat) or 7 days (human) according to the plasma-clot system and CFU-GM for 7 (rat) or 10 (human) days in methylcellulose medium. Cell proliferation was compared between treated and control groups. Our results showed an expected inhibition by the drug of the growth of erythroid progenitors associated to a similar effect on myeloid progenitors. CFU-E and CFU-GM of both human and rat sources were totally inhibited from the concentration of 3.10^{-5} M. The IC_{50} values (approx. 14-20 µM) were consistent with peak rat plasma levels reached *in vivo* by the drug . Therefore, the short-term cloning assays performed on rat bone marrow cells were sensitive indicators of the hematotoxicity of the agent and were predictive for human toxicity. With less than 10 mg of compound, they can be used as investigative tools to rapidly screen candidate drugs for their hematotoxic potential.

<u>Mots-clé</u>: Hematotoxicity; *In Vitro*; Erythroid progenitor; Myeloid progenitor; CFU-E; BFU-E