CHRONOPHARMACOLOGY OF MITOXANTRONE (MX): EVIDENCE FOR A CIRCADIAN RHYTHM OF ITS MYELOTOXICITY FROM AN ANIMAL MODEL AND A CLINICAL PILOT TRIAL

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The dosing time of anticancer agents largely affects both the tolerance and the antineoplastic activity of cytostatic drugs. Considerable circadian variations of these drug effects have been reported for anthracylines such as daunorubicin, doxorubicin, epirubicin and 4'-0-tetrahydropyranyladriamycin. This led us to investigate the chronopharmacologic properties of MX, an anthraquinone with similar properties. Our investigations were conducted in an animal model and a clinical pilot study. 144 $B_6D_2F_1$ mice which were synchronized by standardized 12h:12h light-darkness cycles, were injected a single, potentially lethal i.v. dose of MX (13, 14.5, or 16 mg/kg) at six different time points (8 animals per time point). All mice receiving 13 or 14.5 mg/kg MX survived, if the drug had been injected at 3, 7, 11, or 19 hours after light on (HALO), but 25% died if the same doses had been given at 23 HALO. The administration of 16 mg/kg MX at 3 or 7 HALO respectively killed 100% or 80% of mice, as compared to none (!) following drug dosing at 11 or 15 HALO (X^2= 40; $p<0.001$). In subsequent experiments, 99 $B_6D_2F_1$ mice were injected 14.5 mg/kg at four different time points, and the body weight, WBC, or spleen weight were determined as compared to baseline levels after 5, 9, 14 or 21 days. On d 5, leukopenia varied from -84% at 4 HALO to -34% at 22 HALO, and spleen weight loss varied from -34% (22 HALO) to -83% (14 HALO) ($P<0.01$). On d 9, where the maximal body weight loss occured, this variable was least at 16 HALO (-28%), as compared to -36% at 22 HALO ($P<0.01$). We then conducted a clinical pilot study in 9 cancer patients receiving a combination chemotherapy with MX (8 mg/m^2/d IV, d 1+2) and prednimustin (PM; 100 mg/m^2/d PO, d 1-5). While PM was constantly given at 8h00, the dosing time of MX was changed after each treatment course in each patient (2h00, 6h00, 10h00, 14h00, 18h00, 22h00). Again, a small, but significant circadian variation of the leukocyte nadirs was observed with highest counts at 22h00 and lowest counts at 6h00 (difference 20%; $P<0.05$; Wilcoxon). Taken together, both preclinical and clinical data suggest that the toxicity of MX may be significantly reduced by correct circadian timing of its administration. MX seems to be best tolerated in the second half of the activity span.

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