A Combined Experimental and Mathematical Approach for Molecular-based Optimization of Irinotecan Circadian Delivery

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Résumé en anglais	Circadian timing largely modifies efficacy and toxicity of many anticancer drugs. Recent findings suggest that optimal circadian delivery patterns depend on the patient genetic background. We present here a combined experimental and mathematical approach for the design of chronomodulated administration schedules tailored to the patient molecular profile. As a proof of concept we optimized exposure of Caco-2 colon cancer cells to irinotecan (CPT11), a cytotoxic drug approved for the treatment of colorectal cancer. CPT11 was bioactivated into SN38 and its efflux was mediated by ATP-Binding-Cassette (ABC) transporters in Caco-2 cells. After cell synchronization with a serum shock defining Circadian Time (CT) 0, circadian rhythms with a period of 26 h 50 (SD 63 min) were observed in the mRNA expression of clock genes *REV-ERBα*, *PER2*, *BMAL1*, the drug target topoisomerase 1 (*TOP1*), the activation enzyme carboxylesterase 2 (*CES2*), the deactivation enzyme UDP-glucuronosyltransferase 1, polypeptide A1 (*UGT1A1*), and efflux transporters *ABCB1*, *ABCC1*, *ABCC2* and *ABCG2*. DNA-bound TOP1 protein amount in presence of CPT11, a marker of the drug PD, also displayed circadian variations. A mathematical model of CPT11 molecular pharmacokinetics-pharmacodynamics (PK-PD) was designed and fitted to experimental data. It predicted that CPT11 bioactivation was the main determinant of CPT11 PD circadian rhythm. We then adopted the therapeutics strategy of maximizing efficacy in non-synchronized cells, considered as cancer cells, under a constraint of maximum toxicity in synchronized cells, representing healthy ones. We considered exposure schemes in the form of an initial concentration of CPT11 given at a particular CT, over a duration ranging from 1 to 27 h. For any dose of CPT11, optimal exposure durations varied from 3h40 to 7h10. Optimal schemes started between CT2h10 and CT2h30, a time interval corresponding to 1h30 to 1h50 before the nadir of CPT11 bioactivation rhythm in healthy cells.
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