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Uridine supplementation with Mitocnol attenuates mitochondrial cardiomyopathy induced by zidovudine and zalcitabine

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Purpose of the study

Zidovudine is an antiretroviral nucleoside analogue reverse transcriptase inhibitor (NRTI). Long-term use of zidovudine is linked to a cardiomyopathy and various other tissue toxicities, which are associated with mitochondrial DNA (mtDNA) depletion. Because zidovudine inhibits thymidine kinases, the mechanism of mtDNA depletion may involve a restriction in the availability of phosphorylated pyrimidine nucleosides which are required as mtDNA and mtRNA building blocks. We investigated if the cardiomyopathy is a class effect of antiretroviral nucleoside analogues, and if the mitochondrial cardiotoxicity can be prevented with uridine as a pyrimidine nucleotide precursor.

Methods

Balb/c mice were fed with zidovudine (100 mg/kg/day) or zalcitabine (13 mg/kg/day). Mice were co-treated with or without Mitocnol (340 mg/kg/day), a dietary supplement with high uridine bioavailability. Cardiac muscle was examined after 9 weeks of treatment.

Summary of results

Zidovudine and zalcitabine both induced mitochondrial cardiotoxicity. Compared to untreated controls, the histopathological cardiomyopathy score was increased after treatment with zalcitabine (312%, $p < 0.001$) and zidovudine (540%, $p < 0.001$). Mitochondria were enlarged and their crystal architecture was disrupted. The organelles contained low mtDNA copy numbers (zidovudine 87.1%, $p = 0.02$, zalzitabine 86.4%, $p = 0.01$; compared to controls) and reduced cytochrome C-oxidase (COX) activity. The expression of the mtDNA-encoded COX I subunit, but not of nucleus encoded COX IV protein, was impaired. Uridine supplementation attenuated or normalized all pathology and had no intrinsic effects.

Conclusion

Both zidovudine and zalcitabine induced a mitochondrial cardiomyopathy, which is antagonized by uridine supplementation. The results provide proof of the importance of pyrimidine pools in the pathogenesis of zidovudine cardiomyopathy. As uridine supplementation is tolerated well by humans, this strategy should be investigated in clinical trials.