# Anti-Cancer Prodrug Cyclophosphamide Exerts Thrombogenic Effects on Human Venous Endothelial Cells Independent of CYP450 Activation—Relevance to Thrombosis


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## Abstract

Cancer patients are at a very high risk of serious thrombotic events, often fatal. The causes discussed include the detachment of thrombogenic particles from tumor cells or the adverse effects of chemotherapeutic agents. Cytostatic agents can either act directly on their targets or, in the case of a prodrug approach, require metabolization for their action. Cyclophosphamide (CPA) is a widely used cytostatic drug that requires prodrug activation by cytochrome P450 enzymes (CYP) in the liver. We hypothesize that CPA could induce thrombosis in one of the following ways: (1) damage to endothelial cells (EC) after intra-endothelial metabolization; or (2) direct damage to EC without prior metabolization. In order to investigate this hypothesis, endothelial cells (HUVEC) were treated with CPA in clinically relevant concentrations for up to 8 days. HUVECs were chosen as a model representing the first place of action after intravenous CPA administration. No expression of CYP2B6, CYP3A4, CYP2C9 and CYP2C19 was found in HUVEC, but a weak expression of CYP2C18 was observed. CPA treatment of HUVEC induced DNA damage and a reduced formation of an EC monolayer and caused an increased release of prostacyclin (PGI2) and thromboxane (TXA) associated with a shift of the PGI2/TXA balance to a prothrombotic state. In an in vivo scenario, such processes would promote the risk of thrombus formation.