# Toxicity of clopidogrel and ticlopidine on human myeloid progenitor cells: importance of metabolites

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Ticlopidine and clopidogrel are thienopyridine derivatives used for inhibition of platelet aggregation. Not only hepatotoxicity, but also bone marrow toxicity may limit their use. Aims of the study were to find out whether non-metabolized drug and/or metabolites are responsible for myelotoxicity and whether the inactive clopidogrel metabolite clopidogrel carboxylate contributes to myelotoxicity. We used myeloid progenitor cells isolated from human umbilical cord blood in a colony-forming unit assay to assess cytotoxicity. Degradation of clopidogrel, clopidogrel carboxylate or ticlopidine (studied at 10 and 100 $\mu$M) was monitored using LC/MS. Clopidogrel and ticlopidine were both dose-dependently cytotoxic starting at 10 $\mu$M. This was not the case for the major clopidogrel metabolite clopidogrel carboxylate. Pre-incubation with recombinant human CYP3A4 not only caused degradation of clopidogrel and ticlopidine, but also increased cytotoxicity. In contrast, clopidogrel carboxylate was not metabolized by recombinant human CYP3A4. Pre-incubation with freshly isolated human granulocytes was not only associated with a myeloperoxidase-dependent degradation of clopidogrel, clopidogrel carboxylate and ticlopidine, but also with dose-dependent cytotoxicity of these compounds starting at 10 $\mu$M. In conclusion, both non-metabolized clopidogrel and ticlopidine as well as metabolites of these compounds are toxic towards myeloid progenitor cells. Taking exposure data in humans into account, the myelotoxic element of clopidogrel therapy is likely to be secondary to the formation of metabolites from clopidogrel carboxylate by myeloperoxidase. Concerning ticlopidine, both the parent compound and metabolites formed by myeloperoxidase may be myelotoxic in vivo. The molecular mechanisms of cytotoxicity have to be investigated in further studies.

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