Toxicity of thienopyridines on human neutrophil granulocytes and lymphocytes

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 2363473
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Year 2013
Title Toxicity of thienopyridines on human neutrophil granulocytes and lymphocytes
Journal Toxicology
Volume 308
Pages / **Article-Number** 11-9
Keywords Ticlopidine, Clopidogrel, Clopidogrel carboxylate, Prasugrel, Myelotoxicity, Granulocytes, Lymphocytes
Mesh terms Cells, Cultured; Dose-Response Relationship, Drug; Granulocytes, metabolism; Humans; Lymphocytes, metabolism; Membrane Potential, Mitochondrial, physiology; Neutrophils, metabolism; Reactive Oxygen Species, metabolism; Thienopyridines, toxicity
Thienopyridines can cause neutropenia and agranulocytosis. The aim of the current investigations was to compare cytotoxicity of ticlopidine, clopidogrel, clopidogrel carboxylate and prasugrel for human neutrophil granulocytes with the toxicity for lymphocytes and to investigate underlying mechanisms. For granulocytes, clopidogrel, ticlopidine, clopidogrel carboxylate and prasugrel were concentration-dependently toxic starting at 10μM. Cytotoxicity could be prevented by the myeloperoxidase inhibitor rutin, but not by the cytochrome P450 inhibitor ketoconazole. All compounds were also toxic for lymphocytes, but cytotoxicity started at 100μM and could not be prevented by rutin or ketoconazole. Granulocytes metabolized ticlopidine, clopidogrel, clopidogrel carboxylate and prasugrel, and metabolization was inhibited by rutin, but not by ketoconazole. Metabolism of these compounds by lymphocytes was much slower and could not be inhibited by ketoconazole or rutin. In neutrophils, all compounds investigated decreased the electrical potential across the inner mitochondrial membrane, were associated with cellular accumulation of ROS, mitochondrial loss of cytochrome c and induction of apoptosis starting at 10μM. All of these effects could be inhibited by rutin, but not by ketoconazole. Similar findings were obtained in lymphocytes; but compared to neutrophils, the effects were detectable only at higher concentrations and were not inhibited by rutin. In conclusion, ticlopidine, clopidogrel, clopidogrel carboxylate and prasugrel are toxic for both granulocytes and lymphocytes. In granulocytes, cytotoxicity is more accentuated than in lymphocytes and depends on metabolization by myeloperoxidase. These findings suggest a mitochondrial mechanism for cytotoxicity for both myeloperoxidase-associated metabolites and, at higher concentrations, also for the parent compounds.
Publisher Elsevier
ISSN/ISBN 0300-483X
edoc-URL http://edoc.unibas.ch/dok/A6223511
Full Text on edoc No;
Digital Object Identifier DOI 10.1016/j.tox.2013.03.002
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/23499857
ISI-Number WOS:000321089500003
Document type (ISI) Journal Article