Title	Chloramphenicol succinate a competitive substrate and inhibitor of succinate dehydrogenase: relation to its mechanisms of toxicity
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HO-15 Chloramphenicol succinate a competitive substrate and inhibitor of succinate dehydrogenase: relation to its mechanisms of toxicity

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Objective/Method: Chloramphenicol succinate (CAPS) causes marrow depression and in some cases severe aplastic anaemia. Molecular mechanism of this toxicity is still unknown. We studied Ex-vivo metabolism of this antibiotic by human bone marrow to investigate how it is metabolized and which enzyme is involved. To study metabolism marrow samples were incubated with CAPS. To investigate involvement of succinate dehydrogenase (SDH) in CAPS metabolism, marrow samples and rat liver mitochondria were incubated with CAPS in the presence and absence of a known SDH activators and inhibitors at 37^0C. Detection of metabolites was carried out by HPLC.
Results: In 72 marrow samples, CAPS was slowly metabolized to chloramphenicol (CAP). In 20 marrow samples, flavin adenine dinucleotide (FAD) enhanced CAP formation but reduction of FAD to $FADH_2$ was inhibited. While in 3 samples it was metabolized to CAP, nitroso-CAP and another metabolite. Marrow incubated with FAD (control) showed $FADH_2$ peak. No CAP formation was observed when marrow and CAPS were incubated with malonate and 3-NPA. Mitochondria metabolized CAPS to CAP. FAD, succinate and malonate enhanced CAP formation but reduction of $FADH_2$ was inhibited. While, oxaloacetate, 3-NPA and nitroso-CAP inhibited CAPS metabolism to CAP.
Conclusions: These studies demonstrate that CAPS is a competitive substrate for SDH. In marrow and mitochondria, it is oxidized to CAP by SDH and nitro metabolites formed may be responsible for inhibition of SDH. In some marrows presence of SDH isoenzyme may be responsible for both oxidation and nitroreduction of CAPS to CAP, nitroso-CAP and possibly hydroxylamino-CAP. SDH may be a target for CAPS induced marrow toxicity.