DRUG-DRUG INTERACTION POTENTIAL OF AN ANTHRACYCLINE ANTITUMOR AGENT AMRUBICIN HYDROCHLORIDE (SM-5887) IN COMBINATION THERAPY WITH COP
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In the treatment of amrubicin hydrochloride (CALSED®) for malignant lymphoma, combination therapy with cyclophosphamide, vincristine and prednisolone (COP) is expected. Therefore, we evaluated the possibility of drug-drug interaction between amrubicin and COP.
Pharmacokinetic information about COP obtained from literature searching suggests the involvement of some cytochrome P450 (CYP) isoforms and P-glycoprotein (Pgp) in the disposition of COP. We examined the inhibitory effect of amrubicin on CYP in human liver microsomes. IC50 values of amrubicin for CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) were above 30 µM and the potential of mechanism-based inhibition for CYP isoforms was unlikely. Since free amrubicin concentration in plasma is less than 1 µM, it is thought unlikely that amrubicin inhibits CYP isoforms in clinical treatment. We also investigated an involvement of Pgp on membrane permeation of amrubicin and amrubicinol (an active metabolite of amrubicin), and inhibitory effect of these compounds on digoxin transport mediated by Pgp using MDR1 expressing cells. The results suggest that these compounds are substrates of Pgp, but have little effect on digoxin transport, which indicate their low possibility to inhibit Pgp.
Considering all the results mentioned above, the combination of amrubicin hydrochloride and COP will be unlikely to lead to clinically relevant drug-drug interactions.