高α_1-acid glycoprotein血漿モデル（テレビン油投与ラット）におけるquinidineの体内動態

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The Influence of Increased Plasma Protein Binding on the Disposition of Quinidine in Turpentine-Treated Rats

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Abstract The effect of the increased plasma protein binding of quinidine on its disposition was investigated in turpentine-treated rats, since turatment is known to increase the plasma concentration of α_1-acid glycoprotein which preferentially binds basic drugs. The plasma free fraction of quinidine 16 and 48h after turpentine treatment was decreased by 30 and 76%, respectively, compared to the control value. The treatment did not cause live injury nor alter the hepatic blood flow. The disappearance of quinidine in plqsma after an intravenous injection (3.0,7.0,12.5 mg/kg) was analyzed by a two-compartment open model in both control and turpentine-treated rats. The blood total body clearance (CL_b) of quinidine at 48 h after the treatment was decreased by 30 to 65% in a dose-dependent manner, compared to that in control rats. The distribution volume (V_{dss}) of quinidine (12.5mg/kg) at 16 and 48 after turpentine treatment was decreased by 30 and 79%, respectively.

Hepatic extraction ratio (*HER*) of quinidine, which was determined at steady state blood concentrations from 0.5 to 2.3 μg/ml, was decreased from 0.8 to 0.35 with an increase in the quinidine concentration in control rats. The *HER* value 48 h after turpentine treatment was consistently reduced by 15 to 40% in a concentration-dependent manner compared to the corresponding control value. These findings indicate that the increased plasma binding of quinidine caused a reduction of *HER* of the drug, and the reduced *HER* resulted in the decrease in CL_b

in turpentine-treated rats.

Tissue-to-plasma partition partition coefficient (K_p) for the lung, kidney, spleen, liver and heart, which was determined at a aeeady atate plasma concentration (1 μg/ml), was decreased after the turpentine treatment to the same extent as the decrease in V_{dss} (16 h,28-39%;48 h,76-81%).The k_p value in each tissue was proportional to free fraction of quinidine in the plasma.These resuts suggest that V_{dss} and K_p were reduced due to the increase in the plasma protein binding of quinidine in turpentine-treated rats.

テレビン油の投与は、肝障害を伴わず、その血漿α_1-acid glycoprotein濃度のみを著しく上昇した。Control及びテレビン油投与ラットの間において、血漿α_1-acid glycoprotein濃度とquinidineの血漿蛋白質結合は、相関係数r=0.987という非常に高い相関性を示した。従って、テレビン油投与ラットは、quinideの血漿蛋白質結合率増加による本薬物の体内動態の変化を説明する上で、有用な高α_1-acid glycoprotein血漿モデルであることが示された。高α_1-acid glycoprotein血漿モデルにおいて、quinidineの血漿消失を調べたところ、quinidineのCL_bが、dose-dependentにcontrol群のCL_bに比べ著しく減少した。このことは、高α_1-acid glycoprotein血漿モデルにおけるquinidineの肝抽出率がcontrol群のそれに比べて明らかに減少することからも実証された。

高α-acid glycoprotein血漿モデルでは、quinidineのplasma free fraction(f_p)の減少に伴い、K_P値も減少し、またcontrolラット及び同モデル間におけるquinidingのf_pとK_p値の間には、高い相関性が認められた。以上の結果から、血漿α_1-acid glycoprotein濃度の増加に基づくquinidineの血漿蛋白質結合率増加は、quinidineのV_{dss}の減少のみならずCL_bや肝抽出率の減少にも寄与することことが証明された。

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