EFFECTS OF CYP2C8 INHIBITORS ON REPAGLINIDE METABOLISM
Tomoko Inoue, Michiaki Matsuda, Jin Shimakura, Kiyoshi Natsui, Takanori Hashizume, Masashi Yabuki, Setsuko Komuro
Pharmacokinetics Research Laboratories, Dainippon Sumitomo Pharma Co., Ltd. 1-98 Kasugade-naka 3-chome, Konohana-ku, Osaka, 554-0022, Japan

[Purpose] CYP2C8 is a major enzyme responsible for repaglinide metabolism in human liver microsomes. A clinical data has also shown that co-administration of repaglinide and a CYP2C8 inhibitor, gemfibrozil results in increase of the repaglinide AUC (by about 8-fold). Therefore, there is distinct possibility that other drugs exerting inhibitory effects on CYP2C8 could cause increase of repaglinide plasma concentrations in a clinical setting. In the present study, we applied an in vitro test system to clarify the effects of quinidine and verapamil, confirmed to have inhibitory influence with CYP2C8 probes (paclitaxel and amodiaquine), on repaglinide metabolism.

[Methods] Both time-dependent inhibitory effects and reversible inhibitory effects were evaluated by measuring remaining repaglinide concentrations in reaction mixtures in the presence or absence of inhibitors (substrate depletion approach) by LC-MS/MS.

[Results and Discussion] No time-dependent inhibition was observed with either quinidine (100 µmol/L) or verapamil (10 µmol/L) when compared with control activity. For reversible inhibitory effects, inhibition by quinidine (100 µmol/L) was negligible. Meanwhile, inhibition (50% or greater) was observed when verapamil was used within the range of used concentrations (0-100 µmol/L) and its IC₅₀ was determined to be 38.6 µmol/L. The verapamil concentration, however, was about 200-fold higher than clinical plasma concentration.

[Conclusions] From these results, it is suggested that both quinidine and verapamil are not likely to inhibit repaglinide metabolism in humans.