【S-1】

Risk Management of Drugs in Japan and Specific Concern for Drug Interaction

Ryuichi Hasegawa
Division of Medicinal Safety Science
National Institute of Health Sciences, Japan

Risk management of drugs

New drugs are approved on the basis of efficacy and safety information obtained from pre-approval clinical studies as well as non-clinical studies, however the safety profiles may change over time through expanding their use in terms of patient background and the number of patient administered. Therefore, risk management of drugs after approval must be properly and systematically implemented during their lifetime for the safe use of drugs. Pharmacovigilance activity, a part of risk management of drugs, is to detect and report the adverse drug reactions (ADRs) or any other drug related problems. Serious ADRs are defined as death or life-threaten symptoms, permanent or serious functional damages (including congenital abnormality), symptoms need to be hospitalized or extended hospitalization, and other serious symptoms based on medical point of view. Current major serious ADRs in Japan are Stevens-Johnson syndrome, toxic epidermal necrolysis, rhabdomyolysis, fulminant hepatitis, and hepatic and renal failures.

Routine pharmacovigilance activity for all drugs consists of expedited reporting of ADRs and periodic safety update reporting (PSUR). For the former, pharmaceutical companies have to report unexpected serious ADRs and significant regulatory actions taken in foreign countries within 15 days, and serious but known ADRs and unexpected moderate ADRs within 30 days. PSUR is a reporting system for all the relevant new safety information and summary of the market authorization status, and should be submitted every six months in the first two years after the approval, and then every year until the end of re-examination period. Post-marketing activities other than routine pharmacovigilance activity in Japan have been conducted as the followings, 1. Early Post-marketing Phase Vigilance for all drugs, to direct the medical institutions to the correct use of new drugs and to collect information on serious ADRs for 6 months just after the marketing start, 2.

Drug Utilization Investigation for all drugs, to detect unexpected serious ADRs and profiles of ADRs during re-examination period, 3. Special Investigation for specified drugs, to investigate the efficacy and safety in special patient populations, and 4. Post-marketing Clinical Trials for specified drugs, to conduct certain pharmacoepidemiological studies or interventional studies for clarification of remaining safety and efficacy issues.

Following to the above pharmacovigilance activities and government consultation, many management actions have been conducted. Recent critical actions were voluntary withdrawals of sorivudine in 1994, troglitazone in 2000, phenacetin containing drugs in 2001, cerivastatin in 2001 and phenylpropanolamine containing drugs in 2003, and the instruction of limited prescription and strict care to use gefinitib in 2003.

All governmental managements and the actions taken by companies are disseminated through the websites of Ministry of Health, Labour and Welfare, and Pharmaceuticals and Medical Devises Agency (PMDA), the later being newly established in April 2004.

Since 1991, the international harmonization for new drug development and application has been proceeding by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in Japan, US and EU. As its activity, several guidelines for quality, safety and efficacy have been agreed and some of them are implemented. Using this ICH system, simultaneous new drug approval and marketing over the world will come soon.

Specific concern for drug interaction

Statins (HMG-CoA reductase inhibitors) are one of the most widely prescribed classes of drugs throughout the world, because of their excellent cholesterol-lowering efficacy and overall safety profile. However, rhabdomyolysis is a well known adverse event induced by statins although it is rare but fatal. The incidence of statin-associated rhabdomyolysis in US was 3339 during January 1990 to March 2002, and more than half was associated with cerivastatin treatment. The incidence in one million prescriptions was also the highest for cerivastatin, more than 3, compared with the other statins, less than 0.2. Because of its high incidence of rhabdomyolysis and specific interaction with gemfibrozil, cerivastatin was withdrawn from the market in 2003. Despite gemfibrozil is not available in Japan, similar incidences of statin-associated rhabdomyolysis were estimated by our rough calculation.

Drug-drug interaction is considered to be sometimes associated with critical adverse events.

For example, serious drug-drug interactions have contributed to half of the recent US market withdrawals of approved drugs and nearly 17% of emergency department patients in US were indicated to be taking drug combinations with potential interactions. For cases of statins in US, 55-60% of rhabdomyolysis were considered to be associated with co-administrated drugs such as fibrates, mibefradil, cyclosporine, macrolide antibiotics and so on. Based on clinical evidences in pharmacokinetic interactions of statins, it is considered that a part of rhabdomyolysis may occur by pharmacokinetic interactions with certain drugs.

Atorvastatin, simvastatin and lovastatin are metabolized by CYP3A4, cerivastatin by both CYP3A4 and CYP 2C8, and fluvastatin by CYP2C9, but pravastatin is not metabolized by CYPs. Literature shows CYP3A4 inhibitors such as itraconazole, erythromycin and HIV protease inhibitors, increase the area under plasma concentration (AUC) and the peak of plasma concentration (Cmax) for atorvastatin (up to 4 folds) and simvastatin and lovastatin (more than 10) but not for cerivastatin, fluvastatin or pravastatin. Unexpectedly cyclosporine, known as a CYP3A4 inhibitor, clearly increases AUC and Cmax on all of statins, the mechanism being proposed as an inhibition on organic anion transporting polypeptides in liver by in vitro experiments. Reversely AUC on digoxin, the substrate of P-glycoprotein, slightly increases in combination with atorvastatin or simvastatin. The information on these pharmacokinetic drug-drug interactions with their quantitative data should be properly provided in the package inserts to help healthcare providers because only insufficient information was found in current Japanese package inserts of statins.

In addition to drug-drug interactions on statins, grapefruit juice was also found to increase AUC and Cmax of some statins in the same extent of itraconazole, by a mechanism-based inactivation of intestinal CYP3A4. Furthermore, it was shown that not only grapefruit juice but also sweet orange juice dramatically dropped AUC and Cmax on celiprolol, a β -blocker. These food-drug interactions also may be very important and should be taken into account for safe use of potential drugs.