increase seen with itraconazole. However, the warnings in the package insert are very different, with itraconazole being contraindicated, whereas grapefruit juice and HIV protease inhibitors are listed as precautions. Some discrepancy in the strength of any warnings and reported pharmacokinetic effects may be explicable. For example, although there is no pharmacokinetic interaction data reported for simvastatin and clarithromycin there is a report of rhabdomyolysis associated with combination therapy with the two drugs (72).

Instructions for dosage adjustment in the Japanese package inserts are provided only for one combination of drugs, simvastatin and cyclosporin. In contrast, the USA package inserts provide instructions for five combinations (including one combination with gemfibrozil which is not approved in Japan), sometimes accompanied by quantitative data. Furthermore, the USA package inserts provide more quantitative information for typical CYP inhibitors, even though these interactions are of weak potency. For example, data from two discrepant studies are provided for simvastatin and grapefruit interaction in the USA, whereas the Japanese package inserts just lists the results from the study incorporating higher doses without quantitative data. In addition, the mechanism of action for most drug combinations is not specified in the Japanese package inserts and is expressed merely as 'may increase plasma concentration' or ' risk of rhabdomyolysis'.

Although the published data on interactions, reviewed above, is helpful to health care providers for assessing the significance of any interactions, and for selecting safer alternatives, further studies are required for clarifying the mechanisms of drug interactions. This is especially relevant to interactions with fibrates as these agents may induce rhabdomyolysis by themselves (73) and the data is controversial. Despite numerous reports of rhabdomyolysis associated with combined statin and fibrate therapy (4, 74), any increase in statin's AUC with gemfibrozil is not as high as that seen with macrolides or azole antifungals (50, 60, 75, 76). There is evidence from *in vivo* studies that gemfibrozil alters the pharmacokinetics of other drugs by inhibiting CYP2C9 (77, 78), whereas an *in vitro* study showed that it was unlikely to inhibit other CYP isoforms (79). It has also been shown in human liver microsome that gemfibrozil inhibits glucuronidation of statins and its metabolites by UDP-glucuronyltransferase (UGT) (80). Other fibrates, such as fenofibrate, clofibrate and ciprofibrate are also metabolized by UGT (78), and it is possible that inhibition of this elimination pathway may be a cause of statin-fibrate interactions. Further *in vivo* studies are required to verify this mechanism. A recent *in vitro* study on rosuvastatin, a compound metabolized to a minor degree by CYP2C9 (81), indicated that gemfibrozil may interact with statins via organic anion transporter polypeptides (OATPs). This hypothesis is attractive, as various statins metabolized by different CYPs or indeed unaffected by CYPs, are affected to similar extents by gemfibrozil (82). Despite interactions between certain combinations of statins and fibrates leading to relatively large increases in AUC, this mechanism does not fully explain the marked increase in the prevalence of rhabdomyolysis.

Recently, it has been reported that P-glycoprotein and OATPs also influence the pharmacokinetics of statins, thereby making it difficult to predict quantitative drug interactions from CYP data alone. P-glycoprotein functions as a biological barrier by enhancing the excretion of xenobiotics including drugs from the liver or renal tubules into the adjacent luminal spaces (83). Both CYP3A4 and P-glycoprotein have similar substrates and inhibitor profiles, and many drug interactions involve both of these proteins. For example, cyclosporin is a substrate for both CYP3A4 and P-glycoprotein (84, 85) whereas statins are also substrates (86–89) and inhibitors of P-glycoprotein (90). Other transporters involved in drug pharmacokinetics are OATPs that function as multispecific carriers capable of bi-directional transport across the sinusoidal liver membrane (91). Uptake of statins across this membrane has been shown to be mediated by certain members of the OATP family (92, 93). A recent *in vitro* study suggests that another OATP family protein called OATP-B, located at the apical membrane of small intestinal epithelial cells, mediates pravastatin absorption in a pH-dependent manner (94, 95). These findings indicate that P-glycoprotein and OATPs are crucial for intestinal absorption, hepatic uptake and biliary secretion of statins and concomitant drugs. This mechanism may explain the interaction between cyclosporin and pravastatin or pitavastatin, despite the fact that

neither drugs is metabolized by CYP3A4. There is clearly a need for further information on the role of these transporters in the pharmacokinetics of statins.

The differences in information content of package inserts for each statin between regions may reflect differences in regulatory requirements and timing of drug development. Current guidelines for drug interaction studies were established in 2001 in Japan (96), and in 1997 [*in vitro* (97)] and 1999 [*in vivo* (98)] in the USA. It is possible that license holders may therefore not have conducted pharmacokinetic interaction studies during the drug developmental stage. In addition, most of the interaction studies were published in the late 1990s or thereafter. In our study we did not distinguish whether information contained in the current package inserts was first-time presentations or amended versions. However, license holders have an obligation to provide current scientific knowledge without regard to the date of approval of the drug.

Another difference between the Japanese and USA package inserts was that higher dosages of statins are listed occasionally in the USA package inserts (Table 1). Although this would be expected to result in a lower incidence of drug interactions in Japan, this was not seen possibly because of the lower body weight of Japanese people and the fact that cases of rhabdomyolysis are rare.

One of the characteristics of the Japanese package insert is the use of tables in the drug interaction section to improve clarity. The Japanese guidelines also require the package insert to be 'as simple as possible', leading to Japanese license holders omitting data in order to comply with this requirement. This is generally acceptable, but may have gone too far regarding information on drug interactions with important quantitative information on pharmacokinetic drug interactions missing. We consider that such crucial information should be incorporated in the Japanese package inserts.

CONCLUSION

Many studies have demonstrated pharmacokinetic interactions between statins and CYP inhibitors. In addition, some transporters, P-glycoprotein and OATPs may also contribute to observed pharmacokinetic changes. Japanese package inserts contain an incomplete list of drugs that interact with statins, usually only citing the risk of rhabdomyolysis resulting from an increase in the concentration of the drug in the blood. With a few exceptions, no quantitative information is provided or the potency of the interaction is not documented adequately. In comparison, USA package inserts which list almost identical drug interactions include more quantitative data. We recommend that Japanese package inserts need to reflect current information better including details of the mechanisms of action.

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