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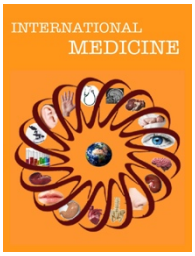

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Editorial

Pharmacological influences of oral hypoglycemic agents (OHAs) for liver function

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Diabetes has been on the rise worldwide and has significant medical and social implications. As to its therapy, the guidelines for the treatment of type 2 diabetes have been compiled in the Europe and United States [1]. Among them, pathological conditions such as insulin secretory capacity and insulin resistance in each patient should be examined [2]. Furthermore, it will be necessary to carry out the medical treatment in consideration of the action mechanism of each agent [3].

There are generally several situations concerning diabetes and liver function. One is the case where obesity was formerly present, accompanied by fatty liver and diabetes [4]. Next is the case where the liver disease was found, associated with type 2 diabetes, which is so-called hepatic diabetes [5]. Hepatitis may also develop during the course of diabetes. Furthermore, there are cases in which fibrosis of the liver progresses and worsens, leading to cirrhosis. As to liver cirrhosis, fibrosis of hepatocytes reduces sugar uptake, forming a portal-systemic shunt. Since glucose flows directly to the peripheral blood without metabolized in the liver, marked hyperglycemia after meals is likely to be observed. In that case, the basic treatment method is the administration of rapid-acting insulin analog three times a day [6]. In contrast, glycogen synthesis and gluconeogenesis are impaired due to a decrease in hepatic parenchymal cells, and then fasting blood glucose shows lower to normal value. In the case of liver cirrhosis, the fluctuation of blood glucose becomes large. This situation tends to show hyperglycemia after eating, and conversely, it tends to become hypoglycemia during the fasting period [7].

Formerly, sulfonylurea (SU) agents were prevalent for the treatment of diabetes. Among them, the second generation glibenclamide and gliclazide have been transferred to the third-generation glimepiride. In both cases, the protein binding rate is high, and due to the decrease in blood albumin, the free molecule may increase in the blood and the hypoglycemic effect may increase [8]. Thus, because of its hepatic metabolism, it is contraindicated in patients with severe hepatic impairment. The glinide agent is a fast-acting insulin secretagogue, which function includes binding to SU receptors and promoting insulin secretion [9]. The rate of excretion in bile is reported as nateglinide 57.5% and repaglinide 95%. In the Child-Pugh classification class B and C of patients with chronic liver disease, obtained data showed 2.5 times in Cmax and 4.3 times in AUCs.

Among dipeptidyl peptidase-4 inhibitor (DPP-4i), there are agents mainly excreted from the kidney as unchanged form and other agents involved in liver metabolism with bile excretion [10]. Urinary excretion and AUC in moderate liver dysfunction shows as follows: 85% vs 1.21 for sitagliptin, 85% vs 0.94 for vildagliptin, 73% vs 1.07 for anagliptin, 72% vs 0.91 for alogliptin, 45% for teneligliptin vs 1.59, linagliptin

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is 5% vs 0.9 [11]. The last linagliptin unexpectedly has a low AUC. One reason for this would be that Cmax is lower than that of healthy adults, suggesting that the proportion of the unchanged drug is as high as 91% of the approximately 80% excreted into feces. Although there is no increase in exposure due to decreased hepatic function, excretion may be inhibited in the pathological condition showing cholestasis.

The biguanide drug metformin has been widely used in the world and is the first line of medication for diabetes [1]. It is mainly absorbed in the small intestine and then excreted from the kidney without metabolism. Therefore, it is considered that the exposure amount itself does not increase due to hepatic dysfunction, and it can be used for mild to moderate hepatic dysfunction [12]. The contraindication includes symptomatic liver dysfunction because of the increased risk of lactic acidosis. It is important to pay attention to the transition of liver function and monitor adverse effects such as gastrointestinal symptoms as the possible initial observation of lactic acidosis [13].

For the thiazolidine agent, pioglitazone has been used in the practice. It can decrease blood glucose level by improving insulin resistance in the periphery and liver, suppressing glucose release from the liver, and the risk of hypoglycemia seems to be low [14]. Serious adverse effects include heart failure, edema, and liver dysfunction. Pioglitazone is metabolized in the liver to produce six types of metabolites. There is a risk of accumulation in patients with severe liver function. As a beneficial effect, improvement of hepatic function and hepatic fibrosis of non-alcoholic steatohepatitis (NASH) has been shown in non-alcoholic fatty liver disease (NAFLD), which may progress to liver cirrhosis and hepatocellular carcinoma [15]. Therefore, it may be used in NASH cases of type 2 diabetes [16].

The α-glucosidase (α-GI) inhibitor is hardly absorbed and metabolized as an unchanged form. Therefore, the amount of α-GI exposed does not increase significantly during liver dysfunction [17]. However, when used in patients with liver cirrhosis, side effects such as constipation may aggravate hepatic encephalopathy [18]. Therefore, the patient has to be observed with attention to abdominal symptoms.

Sodium-glucose co-transporter-2 inhibitor (SGLT-2i) has the effect of lowering blood glucose by suppressing the reabsorption of glucose in the proximal tubule. Currently, several types are clinically applied. Many of them are metabolized by glucuronidation. Since this metabolism is considered to remain even in patients with liver cirrhosis, it is considered that it is difficult to accumulate even if the liver function declines [19]. The AUC and Cmax of four typical drugs, when administered to Child-Pugh classification class B, are shown below, where liver function is moderately impaired [20]. Ipragliflozin is 1.25 vs 1.27, dapagliflozin is 1.359 vs 1.122, canagliflozin is 1.11 vs 0.96, and empagliflozin is 1.47 vs 1.23. In recent years, there have been many reports that SGLT2i is useful for improving liver function in NAFLD / NASH patients [21]. In this sense, it is expected that it will be widely used in clinical settings in the future.

In summary, several topics concerning OHAs and their influences on liver functions were introduced [22]. Some agents possibly show adverse effects of liver dysfunction, and others recently show beneficial effects for NAFLD/NASH. This article will be hopefully useful for research development in the future.

Conflict of interest

The authors declare no conflict of interest.

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