Drug eruption and hepato-renal disorder after treatment with lascufloxacin and suvorexant: drug-drug interaction through cytochrome p450 suspected

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A 55-year-old man feeling a slight fever and malaise visited nearby clinic and he was given lascufloxacin which is a type of quinolone antibiotic. The patient had been taking suvorexant and febuxostat for years, and he had never abnormal blood test results. After starting lascufloxacin treatment, he realized a rash and a rising fever more. He had been taking lascufloxacin for three days when he visited our hospital. A physical examination confirmed the presence of slightly pruritic erythema arising from neck, trunk and extremities. (figure 1a) The blood data revealed hepato-renal failure (AST 71 IU/L, ALT 72 IU/L, Creatinine 2.8 mg/dL) and high CRP (27 mg/dL) with positive procalcitonin (>0.5 ng/mL). Virus infection (influenza, rubeola, Epstein - Barr virus and cytomegalovirus, et all) work- up was negative. Histopathological examination of the erythema skin revealed mild infiltrative eosinophils in the upper dermis with no necrotic epidermal cell. (figure 1b) There were findings of suspected pneumonia in computed tomography image. We considered that he suffered from bacterial pneumonia and toxic eruption complicating hepato-renal side effects. He was hospitalized with vancomycin and meropenem intravenous feeding. And we stopped all oral drugs that he had been taking so far, suspecting that there was a possible of drug-drug interactions between lascufloxacin and suvorexant. The temperature went down and the eruption disappeared in few days. The condition improved and he left hospital 18 days after being hospitalized. The patch testing of lascufloxacin and suvorexant was negative. We underwent drug-induced lymphocyte stimulation test against febuxostat only and it was negative. He sometimes takes suvorexant for insomnia as oral loading test, blood data shows just mild elevation of hepatic deviation enzyme and he has neither

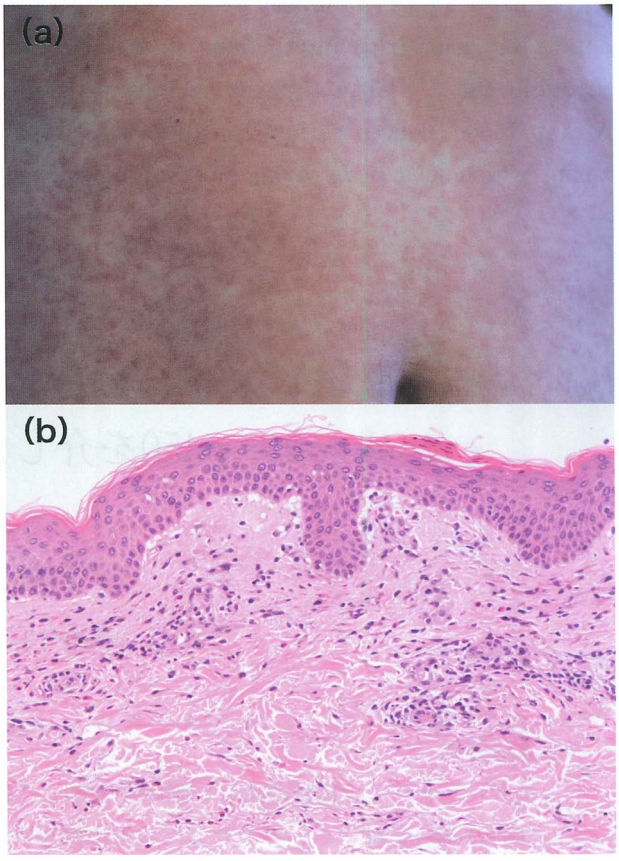

Figure 1.
(a) There is slightly pruritic erythema at the patient's trunk.
(b) Histopathological examination of the erythematous reveals that eosinophils infiltrate in the upper dermis and no necrotic epidermal cell (hematoxylin-eosin [HE], original magnification ×200).

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eruption nor fever. He has decided not to take lascufloxacin.

Suvorexant a novel, orexin receptor antagonist was approved for the treatment for insomnia in 2014.[1] This acts by blocking the orexin system, therefore reducing arousals and improving sleep consolidation. This is metabolized by the cytochrome P450 isoenzyme CYP3A4 systems mainly, resulting in an inactive hydroxyl-suvorexant metabolite and is evacuated mainly through the feces and the urine.[2] CYP3A4 inhibitor drugs are involved this metabolism of suvorexant and raise the medicine blood concentration. Package insert of suvorexant mentions that CYP3A4 inhibitors, itraconazole, clarithromycin, ritonavir, nelfinavir and voriconazole are contraindications for coadministration, but few clinicians know the fact. Lascufloxacin, a new type of quinolone antibiotics, is also CYP3A4 inhibitor drug. Thus, there is doubt for drug-drug interactions in our patient through the CYP3A4 system increasing suvorexant blood concentration by taking lascufloxacin, which is a novel drug and not mentioned to use caution with suvorexant. It is expected that the metabolic abnormalities are different at the individual gene level because of the low incidence of drug disorders although many such incidents should occur in the clinical situation. Actually, it is reported that the metabolism level by CYP3A4 varies depending on races and individuals.[3]

It should be noted that other drugs which are metabolized via the CYP3A4 system may interact with suvorexant and should be used with caution.

Conflict of interest: None declared

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スボレキサントとラスクフロキサシンによるcytochrome p450を介した薬剤性肝腎障害を疑う１例

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スボレキサントは比較的新しい睡眠導入剤で，CYP3A4を強く阻害する薬剤（クラリスロマイシンなど）は本剤の薬効を著しく上昇させるため併用禁忌とされているが，その認知度は低い。この度，ニューキノロン系抗生物質であるラスクフロキサシン錠との併用により薬剤性肝腎障害をきたした症例を経験したので報告する。併用禁忌や注意に記載されてないが添付文書の相互作用にCYP3A4の文言がある場合は慎重投与が望ましい。

Key words：薬疹，スボレキサント，ラスクフロキサシン，cytochrome p450