中文題目：COVID 患者的不明原因休克

英文題目：Profound Shock in An Old Lady with COVID-19: Complex Drug-Drug Interaction of Nirmatrelvir/Ritonavir

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Introduction

Nirmatrelvir/ritonavir is approved for mild-to-moderate COVID-19 treatment via emergency use authorization on December 22, 2021. However, ritonavir-drug interactions with concurrent medications may result in potentially life-threatening adverse effects. Herein, we presented a case of profound shock due to complex drug-drug interaction of Nirmatrelvir/Ritonavir.

Case presentation

An 81-y-old lady presented to our emergency room with severe dizziness and general weakness. She had been suffering from cough and rhinorrhea for 2 d and had been diagnosed with coronavirus disease 2019 (COVID-19) 1 d earlier via rapid antigen test. To combat the viral infection, she received the antiviral agent nirmatrelvir/ritonavir (Paxlovid®) from the medical clinic and the herbal formula Taiwan Chingguan Yihau (NRICM101) from her relatives, one dose each, last afternoon but omitted subsequent doses due to extreme weakness. She had a history of hypertension and was on medication that included benidipine hydrochloride (4 mg daily), bisoprolol (1.25 mg daily), and candesartan/hydrochlorothiazide (16 mg/12.5 mg daily). She denied any food or drug allergy history.

Physical examination revealed a normal body temperature (35.5°C), but extremely low blood pressure (63/29 mmHg), relative bradycardia (57 beats/min), and impaired peripheral circulation (pulse oximeter saturation 92%) raised the possibility of a medical emergency. A crystalloid fluid challenge was given in vain. High dose vasopressor and inotropic agent infusion with norepinephrine(0.2 μg/Kg/min) and epinephrine (0.2 μg/Kg/min) was applied to maintain adequate blood pressure and improved pulse oximeter saturation up to 98% shortly after hemodynamic stabilization. Her respiratory pattern was smooth throughout the resuscitation, with no noticeable wheeze or rhonchi on auscultation. She denied any abdominal pain, tarry stool, or subcutaneous ecchymosis. The laboratory testing showed no leukocytosis (7270/μL), normal C-reactive protein (5.1 mg/L), hyponatremia (128 mmol/L), hypokalemia (3.2 mmol/L), elevated lactate level (4.6 mmol/L), and impaired renal function (creatinine 1.11 mg/dL). The baseline chest radiograph revealed cardiomegaly with no significant infiltration defined. The electrocardiogram (ECG) showed sinus bradycardia and right bundle branch block, but no evidence of myocardial ischemia.

No evidence of the usual cause of profound shock, including septic shock, hypovolemic shock, or obstructive shock, was identified after a comprehensive evaluation. Catastrophic hypotension was observed as a result of drug–drug interaction (DDI) between nirmatrelvir/ritonavir,

benidipine, and the herbal formula NRICM101. Supportive care was given with vasopressors and inotropic agents tailored according to arterial blood pressure. Blood pressure gradually normalized, and urine output and peripheral circulation improved. No more hypotension episode was found during hospitalization.

Discussion

Nirmatrelvir, a potent inhibitor of cysteine protease enzyme and subsequent coronavirus replication, is metabolized mainly by CYP3A4. The ritonavir component is intended to improve nirmatrelvir pharmacokinetics through CYP3A4 inhibition[3]. However, ritonavir-drug interactions with concurrent medications metabolized by the CYP3A4 enzyme may result in unacceptable high serum concentrations and potentially life-threatening adverse effects[4].

Taiwan Chingguan Yihau (National Research Institute of Chinese Medicine 101, NRICM101), a novel traditional herb formula developed by the National Research Institute of Chinese Medicine of Taiwan, is broadly used in Taiwan during the pandemic since April 2020. Huang Qin, or Scutellaria baicalensis Geprgi, is one of the 10 natural plant components in NRICM101 and exhibits the strongest CYP3A4 inhibition ability among 50 herbal medicines in vitro and in vivo[6]. No clinical research was available for the evaluation of possible DDI between NRICM101 and other concomitant medications. However, due to the potential powerful coinhibition of CYP3A4, the Taiwan Centers for disease control has announced no recommendation on the concurrent use of nirmatrelvir/ritonavir and NRICM101.

Calcium channel blockers (CCB), a commonly used antihypertensive, are mainly metabolized by CYP3A4. Several case reports about antiviral drug interactions with CCBs via CYP3A4 inhibition remind us of the common but potentially fatal adverse effects, such as hypotension, bradycardia, and acute renal failure (Table 1).

In our patient, profound shock occurred soon after only one dose of both nirmatrelvir/ritonavir and NRICM101. No identifiable etiology had been recognized after comprehensive evaluation except complex DDI between nirmatrelvir/ritonavir, NRICM101, and benidipine via the CYP3A4 inhibition pathway. Ritonavir-associated CYP3A4 inhibition is rapid-onset with maximum inhibitory effect within 48 h[8]. Concomitant use of the herb formula NRICM101 may enhance the robust CYP3A4 inhibition, resulting in significantly elevated serum benidipine concentrations and clinical profound shock.

Of note, there are still unmet clinical needs challenging our practice. First, not every drug possessing potential DDI is listed on the screening table. Second, over-the-counter medicine, including herb formulas and recreational drugs, may complicate the complexity of DDI. Third, the elderly and inadequate health literacy may play a tremendous barrier between medical advice and drug compliance. Unfortunately, the same population is also the high-risk group that needs antiviral agents the most. Elderly and patients with inadequate health literacy may be hard to follow specific dose adjustment advice which lead to life-threatening DDI despite the doctor noticing and responding appropriately to potential DDI.

Conclusion

Our case report points out the critical aspect of complex drug-drug interaction between nirmatrelvir/ritonavir and concurrent medication. Concomitant use of ritonavir and Scutellaria baicalensis Geprgi in herb formula NRICM101 contribute to the powerful CYP3A4 inhibition and resulting in accumulating benidipine vasodilation effect and profound shock. Timely recognition leads to the correct discontinuation of the offending drug and avoidance of unnecessary invasive investigation. Besides universal DDI screening resources, clinical vigilance and local customs awareness are also crucial in the prevention of potentially fatal side effects. More dedicated research and organized algorithm are needed to safely prescribe those life-saving antiviral agents during a pandemic.

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