Letter to the editor

COVID-19 & antiepileptic drugs: Should we pay attention?

Dear Editor,

People with novel coronavirus disease (SARS-CoV2) may have hypoxia, multi-organ failure, meningitis, encephalitis, and severe metabolic and electrolyte imbalance. Therefore, these patients are expected to have clinical or subclinical acute symptomatic seizures, especially during the intensive care unit (ICU) admissions. It was determined that 25% of COVID-19 patients had central nervous system (CNS) manifestations and 2% of them had at least one seizure during treatment process [1]. Drug-drug interactions (DDIs) with high clinical significance between antiepileptic drugs (AEDs) and anti-COVID-19 therapies (antiviral and immune therapies) were evaluated in this letter.

Pharmacokinetic DDIs between AEDs and anti-COVID-19 therapies (antiviral and immune therapies) may pose clinically significant challenges. According to the list that was prepared by The Liverpool Drug Interaction Group, DDIs between some medications used in COVID-19 and AEDs may lead to drug-related problems such as toxicity, treatment failure, increasing adverse effects and seizure frequency. For example, carbamazepine (CBZ) and lopinavir/ritonavir (LPV/r) or atazanavir (ATV) combination may result in a marked decrease in concentrations of LPV/r or ATV and increased concentrations of CBZ due to CYP3A4 inhibition. If CBZ is combined with a twice-daily LPV/r, monitor for reduced LPV/r effectiveness. Increased LPV/r dose is not an appropriate option to manage this interaction, due to higher doses of LPV/r is associated with a higher risk of liver and gastrointestinal toxicity. Therefore, coadministration should be avoided unless judged strictly necessary to avoid virological failure which has clinical implications for disease progression and development of LPV/r or ATV resistance in COVID-19 therapy [2]. Additionally, compared to monotherapy with AEDs, using dual antiepileptic treatment may increase DDIs risk and lead to treatment failure and toxicity.

Phenytoin possibly reduces LPV/r serum levels by 30%. Therefore, COVID-19 patients with epilepsy receiving phenytoin may require a LPV/r dosage increase of about 50% to maintain unchanged serum concentrations [3]. At the same time, coadministration of LPV/r and valproic acid increased LPV/r area under the curve (AUC) by 38%, while LPV/r causes a 48% reduction in valproic acid serum concentrations. A similar situation exists for lamotrigine. If these AEDs are used with LPV/r, a dose increase of valproic acid or lamotrigine may be required [2]. In addition, concomitant use of azithromycin and hydroxychloroquine with some AEDs (e.g. lacosamide, phenobarbital, primidone rufinamide, phenytoin, and CBZ) increases the risk of cardiac conduction abnormalities (e.g., AV block) and QT/PR interval prolongations. Another point to be mentioned is since hydroxychloroquine has very long half-lives (30–60 days), and DDIs may occur even after discontinuation of treatment [1]. Moreover, concomitant use of eslicarbazepine and ATV or LPV/r may lead to QT prolongation but oxcarbazepine that is the active metabolite of CBZ have no effect on QT interval [3]. If these drugs are considered useful, the risk/benefit ratio has to be evaluated and individualized treatment options should be assessed [4]. Therefore, co-administration of these two groups of drugs should be done cautiously with ECG monitoring. As a result, Tisdale risk score for QT prolongation [5], and evidence-based current and scientific databases are strongly recommended to evaluate the clinical significance of these DDIs with a patient-centered approach. If these drugs are considered beneficial, the risk/benefit ratio should be evaluated, and individualized treatment options should be evaluated accordingly.

DDIs between benzodiazepines (diazepam, clobazam, clonazepam) which use in acute seizure management and ATV, Darunavir/Cobicistat or LPV/r may increase benzodiazepines’ serum levels and risk of toxicity [2]. Using alternative agents or monitoring closely in terms of benzodiazepine toxicity is a rational approach for the management of acute seizures in patients with COVID-19.

The general approach to epilepsy treatment is to reduce the frequency of seizures by using antiepileptic drugs rationally. However, some drug-related problems in antiepileptic drug use such as DDIs, adverse effects, and toxicity can cause difficulties in rational drug use. During the treatment of COVID-19, concomitant use of high-risk medications such as AEDs should be evaluated carefully in terms of DDIs to avoid any negative outcomes such as toxicity or treatment failure in the treatment process.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

References

