Letter

Benefit versus toxicity risk of digoxin in patients with COVID-19

As the oldest cardiac glycoside with a narrow therapeutic index and complex pharmacokinetic profile, digoxin is still used to treat many conditions such as congestive heart failure (CHF), atrial fibrillation or flutter, and certain cardiac arrhythmias.[1] Its distribution in the heart and muscles might increase due to hyperthyroidism or hypokalaemia and decrease due to hyperkalaemia or hyponatraemia.[1] Digoxin is the minor substrate of cytochrome-P450 (CYP) 3A4 and the major substrate of P-glycoprotein/ABCB1.[1]

In general, the incidence of toxicity is reported to be about 1% in patients with CHF treated with digoxin.[1] Increased intracellular calcium due to inhibition of Na–K transporter is the primary pathway of digoxin toxicity.[2] Factors such as renal function, age, lean body weight, cytokine levels and concomitant medications should be considered carefully during digoxin treatment to minimise toxicity.[1] Digoxin toxicity may cause various electrocardiographic changes.[2] The common signs of digoxin toxicity include nausea, vomiting, abdominal pain, yellow vision, headache, lethargy confusion, dizziness and delirium.[2]

The beneficial effect of digoxin in patients with COVID-19 and atrial arrhythmias has been reported. Several studies have also reported on the antiviral and anti-inflammatory properties of cardiac glycosides via inhibition of the entrance of coronavirus into the cells and suppression of a cytokine storm.[3]

However, concerns for digoxin use in patients with COVID-19 include issues such as the risk of an interaction between digoxin and the drug used for the treatment of COVID-19, inhibition of digoxin metabolism due to increased cytokine levels during COVID-19 infection, and atrial fibrillation and electrolyte imbalance due to COVID-19 itself. Therefore, in spite of the antiviral and anti-inflammatory benefits of digoxin in patients with COVID-19, the need for frequent monitoring of the digoxin level should be considered.

Medications used in COVID-19 treatment such as hydroxychloroquine, azithromycin or lopinavir/ritonavir inhibit the enzymes that are responsible for medication metabolism leading to digoxin toxicity.[2 3] In a cohort of 1001 elderly patients, digoxin was found to be the most common drug to interact with hydroxychloroquine, indicating the need for a closer level of monitoring.[4]

Moreover, it is reported that patients with COVID-19 experience electrolyte disturbances, particularly hypokalaemia. Thus, COVID-19 patients using digoxin for CHF are at increased risk of digoxin toxicity and serum digoxin levels should be closely monitored.[2] Furthermore, atrial fibirllation and flutter were observed in 16% of hospitalised patients with COVID-19 and 60% of arrhythmias were reported as new onset.[3] However, due to the high mortality risk, atrial fibrillation and flutter should be treated, even with the risk of drug toxicity.

Inflammation is another concern, and extreme increases in cytokine levels in patients with COVID-19 may result in organ damage to the lung, heart and liver due to suppressed CYP enzymes. Since the liver is the main organ responsible for protein synthesis and the primary site of CYP-mediated drug metabolism, even a minor change in liver function has the potential to affect digoxin toxicity.[5]

As a result, in spite of the potential benefits of digoxin in patients with COVID-19, special consideration should be given to patients receiving treatment with digoxin regarding the effect of COVID-19 itself (disease stage, electrolyte disturbance, organ damage especially liver) and concomitant usage of COVID-19 medications in order to avoid digoxin toxicity.

Burcu Kelleci Cakir ,
Aygin Bayraktar-Ekincioglu, Kutay Demirkan

Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara, Turkey

Correspondence to Mrs Burcu Kelleci Cakir, Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, 06100 Ankara, Turkey; burcukelleci@hacettepe.edu.tr

Contributors All authors contributed equally.

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ORCID iD
Burcu Kelleci Cakir http://orcid.org/0000-0003-2547-8919

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