Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Potential interactions between COVID-19 vaccines and antiepileptic drugs

Fırat et al. [1] discussed the potential drug-drug interactions between antiepileptic drugs and therapeutic drugs currently used in the management of coronavirus disease 2019 (COVID-19). This piece of discussion is relevant and indeed is of utmost importance given that clinicians specialized in the management of COVID-19 may not be familiar with the use of antiepileptic drugs and thus they may be of little knowledge how best to manage the potential drug-drug interactions involving antiepileptic drugs and the therapeutic drugs for COVID-19. While we compliment the effort by Fırat et al. [1], we believe that in the current context where COVID-19 vaccines had been administered to the public in few countries, and soon to be distributed all around the world, we should discuss the potential interactions between COVID-19 vaccines and antiepileptic drugs.

Many may not know that vaccines could modify the metabolism of the drug in the human body. Upon vaccination, an immune response that closely replicates the natural immune response to the infectious disease would be elicited, which serves to protect against the infection by the same or closely related pathogens. In contrary to our common belief, such an immune response does not merely involve the humoral arm of the immune system where B lymphocytes are triggered to produce antibodies, but it also involves the cellular arm of the immune system mediated by T lymphocytes to produce cytokines, most notably interferon-gamma [2].

Specifically, administration of the COVID-19 vaccine BNT162b2 elicited strong antibody responses alongside robust CD4+ and CD8 + T-cell responses, where expansion of CD4+ and CD8 + T cells was observed, with a high fraction of these spike (S) protein-specific T-cells producing interferon-gamma [3]. In addition, administration of the COVID-19 vaccine mRNA-1273 CD4+ also elicited T-cell responses that produced interferon-gamma upon stimulation with S-specific peptides [4]. T-cell responses with the production of interferon-gamma are not specific to mRNA vaccines (BNT162b2, mRNA-1273), in which the vector-based COVID-19 vaccine ChAdOx1 nCoV-19 had been demonstrated to elicit similar responses [5].

Cytokines such as interferon-gamma could lead to reduced expression of cytochrome P450 (CYP) enzymes. An *in vitro* study [6] with human hepatocytes reported that exposure to interferon-gamma led to downregulation of CYP 1A2 and CYP 3A4. In addition, activities of CYP enzymes, as measured by the erythromycin breath test, inversely correlated with interferon-gamma production after administration of vaccine [7]. However, not all CYP enzymes could be affected by the production of interferon-gamma, wherein *in vitro* studies demonstrated that human hepatocytes treated with interferon-gamma had reduced expression for CYP 1A2, CYP 2C8, CYP 3A4, CYP 2B6, CYP 2E1, but no effect on the expression for CYP 2C9, CYP 2C19, and CYP 2C18 [6,8,9].

Antiepileptic drugs vulnerable to interactions with COVID-19 vaccines include carbamazepine, which is metabolized by the hepatic CYP 3A4 enzymes [10]. There had been a case report [11] of carbamazepine toxicity that developed 13 days following administration of the influenza vaccine. Besides, a case series [12] found that serum phenytoin levels that increased temporarily by 46–170 % in certain patients could best be attributed to the influenza vaccination. The interaction with phenytoin is probably not as significant compared to carbamazepine since phenytoin is largely metabolized by CYP 2C9 and CYP 2C19 which the levels are not affected by interferon-gamma, while a minor fraction is metabolized by CYP 2C8 [10]. In another prospective study [13] of 55 patients, mean serum concentrations of phenytoin and phenobarbital were significantly higher than baseline on day 7 after administration of influenza vaccine, while mean serum concentration of carbamazepine significantly increased from day 7 to day 14 after administration of influenza vaccine. Of note, phenobarbital is largely metabolized by hepatic CYP 2C9 with minor metabolism by CYP 2C19 and CYP 2E1 [10]. Other antiepileptic drugs such as ethosuximide (metabolized by CYP 3A4, CYP 2E), clonazepam (metabolized by CYP 3A4), felbamate (metabolized by CYP 3A4, CYP 2E1), tiagabine (metabolized by CYP 3A4), and zonisamide (metabolized by CYP 3A) may also be susceptible to the interaction with COVID-19 vaccines, though there are no previous reports of drug-vaccine interaction involving these drugs [10].

Although the currently available studies involve interactions between influenza vaccines and antiepileptic drugs, it appears reasonable to assume that the same could occur with COVID-19 vaccines due to interferon-gamma production from T-cell responses elicited by COVID-19 vaccines. Certainly, more studies are needed to investigate the potential interactions between COVID-19 vaccines and antiepileptic drugs, including if the effects differ between different types of COVID-19 vaccines. However, our concerns of potential interactions between COVID-19 vaccines and antiepileptic drugs should not be interpreted as a reason for patients with epilepsy to avoid COVID-19 vaccination or that the COVID-19 vaccination would be less effective. Instead, in the meantime, the clinicians should be vigilant towards such interactions, and patients should be advised to report symptoms of hypertoxicity, before the establishment of the clinical relevance of our concerns in the future studies.

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Chia Siang Kow*

School of Postgraduate Studies, International Medical University, Kuala Lumpur, Malaysia

Syed Shahzad Hasan[a,b]

[a] *School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom*

[b] *School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, Australia*

* Corresponding author.

E-mail address: chiasiang_93@hotmail.com (C.S. Kow).