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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Testing of human equivalent dose of health food 5-aminolevulinic acid using the experimental pig

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Dear Editor:

Updated consolidated information on potential drugs to prevent the spread of coronavirus disease (COVID-19) and to treat patients worldwide is essential [1]. While there have been few effective medications for the novel coronavirus infection, the use of drugs that have previously been approved for other indications and with known efficacy is advancing rapidly [2–5]. However, their use is considered to be limited by anti-SARS-CoV-2 50% maximal effective concentrations (EC_{50}) that exceeded their achievable peak serum concentrations (Cmax), side effects, and availability. Recently, Yuan et al. reported a two-tier drug screening system that combined the SARS-CoV-2 enzyme-linked immunosorbent assay and cell viability assay and applied it to screen a library consisting 1528 Food and Drug Administration-approved drugs [6].

In addition, health foods that are being widely consumed by people and have no or very few adverse events are also attracting attention as treatments for the novel coronavirus infection. A recent in vitro experiment showed the virucidal effect of 5-aminolevulinic acid (5-ALA) such health foods on SARS-CoV-2, and clinical trials are currently under way [7]. ALA is widely used as a health food, and there have been no reports of adverse events related to its use. However, the virucidal effect on the coronavirus mentioned in the previous study is based on culture solution observations, and to achieve the same concentration of ALA in blood, the dose must be raised to 15–45 times that of the oral intake of health foods. In fact, a recent case report concerning patients with coronavirus mentioned that empirically, the ALA dose used was 750–2250 mg/day [8].

We previously verified the human equivalent dose (HED) of 5-ALA to determine the various unknown effects of health foods in an experimental miniature porcine kidney ischemia/reperfusion model that is physiologically similar to humans [9]. First, we pre-administered the porcine kidneys with a high concentration of ALA, at 10 times more than the amount used in human health foods (low concentration), to induce an extremely ischemic state in the kidneys and determined the concentration that achieves a clear pathological improvement. Our results indicated that the pathological score improved in a dose-dependent manner in the porcine model. We also observed a correlation between the blood 5-ALA concentration and pathological score for each animal. Therefore, we estimated the required blood 5-ALA concentration from the expected pathological score using the approximation formula and used the results of pharmacokinetic testing in a human phase 1 study (5-ALA administered dose – blood concentration curve) to calculate the predicted effective dose of 5-ALA for clinical use in humans (Fig. 1).

Pharmacokinetic and pharmacodynamic testing is not required for common health food products. While health foods may contain both effective and potentially harmful components, they are not subjected to thorough evaluation procedures such as measurement of the postprandial blood concentration of their components and evaluation of their blood-concentration-related effects. However, when attempting to rapidly verify the secondary pharmacological effect of health foods, such as their virucidal effect on the novel coronavirus, it would be difficult to extrapolate the knowledge on the pharmacological effect of the health foods gained using cultured cells and mice to humans; mice data cannot be extrapolated to humans with accurate predictability.

In this regard, it may be necessary to determine the human equivalent dose of such health foods by evaluating their secondary pharmacological effects other than the antiviral effect using experimental pigs that are similar to humans in terms of body size and metabolism. The use of pigs would allow us to observe the adverse effects of test compounds and alert physicians of possible concentration-related effects when the products are used in the human clinical setting. A recent study indicates that swine are susceptible to low levels of SARS-CoV-2 viral infection [10]. Infectious dose, viral isolate, age, comorbidities such as risk factors for severe COVID-19 in humans, and breed or colony of pigs could affect outcomes. Pigs with risk factors for severe COVID-19 in humans may facilitate and accelerate SARS-CoV-2/COVID-19 research.

Ethics approval and consent to participate

All experiments were performed in accordance with the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions issued by the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Principles of Laboratory Animal Care (NIH publication

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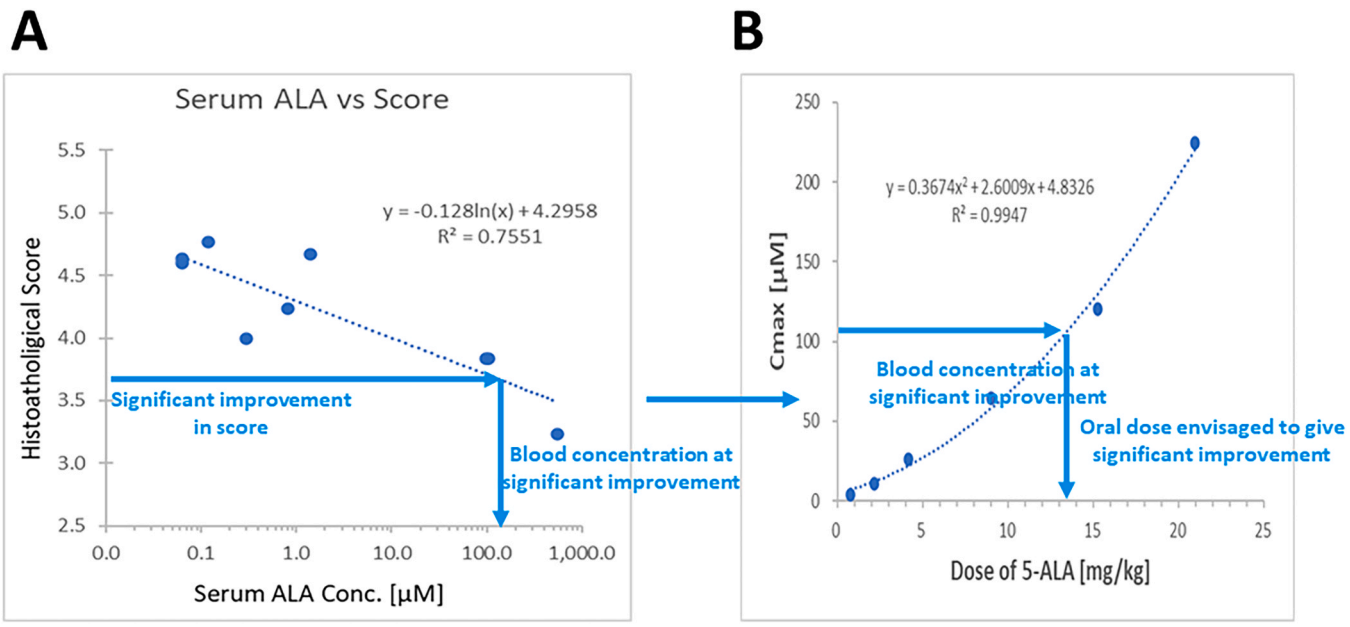

(Modified from Fujine K, et al. Predicting the Effective Dose of 5-Aminolevulinic Acid to Protect Humans From Renal Ischemia-Reperfusion Injury: A Study in Micro Miniature Pigs. 11(1), 8-14.. J Curr Surg. 2021. Fig. 4 . Copyright 2020 Fujine et al. Used under the Creative Commons Attribution-NonCommercial 4.0 International License: https://creativecommons.org/licenses/by-nc/4.0/).

Fig. 1. (A): First, a fitted line was used to estimate the porcine blood concentration of 5-aminolevulinic acid (5-ALA) at which there was a significant improvement in pathological score in the porcine ischemia/reperfusion model. (B): A fitted curve is shown for maximum 5-aminolevulinic acid (5-ALA) blood concentration (Cmax) (vertical axis) plotted against oral dose of 5-ALA (horizontal axis) in healthy people. This fitted curve was used to extrapolate the oral dose in humans that corresponded with the 5-ALA blood concentration in pigs at which there was significant improvement.

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Declaration of Competing Interest

None.

References

[1] W.G. Dos Santos, Natural history of COVID-19 and current knowledge on treatment therapeutic options, Biomed. Pharmacother. 129 (2020), 110493, https://doi.org/10.1016/j.biopha.2020.110493.

[2] R. Parra-Medina, J.C. Sarmiento-Monroy, A. Rojas-Villarraga, E. Garavito, G. Montealegre-Gómez, A. Gómez-López, Colchicine as a possible therapeutic option in COVID-19 infection, Clin. Rheumatol. 39 (2020) 2485–2486, https://doi.org/10.1007/s10067-020-05247-5.

[3] M. Hoffmann, S. Schroeder, H. Kleine-Weber, M.A. Müller, C. Drosten, S. Pöhlmann, Nafamostat mesylate blocks activation of SARS-CoV-2: New treatment option for COVID-19, Antimicrob. Agents Chemother. 64 (2020), e00754-20, https://doi.org/10.1128/AAC.00754-20.

[4] K. Sharun, K. Dhama, S.K. Patel, M. Pathak, R. Tiwari, B.R. Singh, R. Sah, D. K. Bonilla-Aldana, A.J. Rodriguez-Morales, H. Leblebicioglu, Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19, Ann. Clin. Microbiol. Antimicrob. 19 (2020) 23, https://doi.org/10.1186/s12941-020-00368-w.

[5] P.-T. Diep, Oxytocin may be superior to gliptins as a potential treatment for diabetic COVID-19 patients, SciMed. J. 2 (2020) 106–107, https://doi.org/10.28991/SciMedJ-2020-02-SI-10.

[6] S. Yuan, J.F.W. Chan, K.K.H. Chik, C.C.Y. Chan, J.O.L. Tsang, R. Liang, J. Cao, K. Tang, L.L. Chen, K. Wen, J.P. Cai, Z.W. Ye, G. Lu, H. Chu, D.Y. Jin, K.Y. Yuen, Discovery of the FDA-approved drugs bexarotene, cetilistat, diiodohydroxyquinoline, and abiraterone as potential COVID-19 treatments with a robust two-tier screening system, Pharmacol. Res. 159 (2020), 104960, https://doi.org/10.1016/j.phrs.2020.104960.

[7] Y. Sakurai, M.M. Ngwe Tun, Y. Kurosaki, T. Sakura, D.K. Inaoka, K. Fujine, K. Kita, K. Morita, J. Yasuda, 5-Amino levulinic acid inhibits SARS-CoV-2 infection in vitro, Biochem. Biophys. Res. Commun. 545 (2021) 203–207, https://doi.org/10.1016/j.bbrc.2021.01.091.

[8] M. Nakajima, K. Kaketani, Safety, tolerability, and efficacy of 5-aminolevulinic acid phosphate, an inducer of heme oxygenase 1, in combination with sodium ferrous citrate for the treatment of COVID-19 patients, Open Sci. Framew. (2021), https://doi.org/10.31219/osf.io/azxsm.

[9] K. Fujine, M. Sano, Y. Katsumata, K. Sato, E. Kobayashi, Predicting the effective dose of 5-aminolevulinic acid to protect humans from renal ischemia-reperfusion injury: a study in micro miniature pigs, J. Curr. Surg. 11 (2021) 8–14, https://doi.org/10.14740/jcs429.

[10] B.S. Pickering, G. Smith, M.M. Pinette, C. Embury-Hyatt, E. Moffat, P. Marszal, C. E. Lewis, Susceptibility of domestic swine to experimental infection with severe acute respiratory syndrome Coronavirus 2, Emerg. Infect. Dis. 27 (2021) 104–112, https://doi.org/10.3201/eid2701.203399.

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