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High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia

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A B S T R A C T

Background: Pulmonary hypertension is a significant complication for some patients with COVID-19 pneumonia, especially those requiring intensive care. Tachyphylaxis to the current therapy, inhaled nitric oxide (iNO), is also common. In vitro, folic acid directly increases nitric oxide (NO) production and extends its duration of action; effects which could be of benefit in reversing pulmonary hypertension and severe hypoxaemia. Our work has shown that, in the systemic circulation, folic acid in high dose rapidly improves nitric oxide mediated vasodilation, by activating endothelial nitric oxide synthase (eNOS).

Hypothesis: A similar effect of high dose folic acid on pulmonary endothelial function would be expected from the same mechanism and would lead to improvement in pulmonary perfusion. We therefore hypothesise that folic acid, 5 mg or greater, is a useful therapeutic option for pulmonary hypertension and/or refractory severe hypoxaemia, in patients with severe COVID-19 associated pneumonia in whom NO therapy is considered, with a very low risk of adverse effects.

Introduction

Pulmonary Hypertension may be primary or secondary to a variety of underlying pulmonary, cardiovascular or systemic conditions [1,2]. In persistent pulmonary hypertension of the newborn (PPHN), inhaled nitric oxide (iNO) therapy is well established. Pulmonary hypertension occurs as a complication of severe pneumonia and there are reports of it complicating severe COVID-19 pneumonia. Both iNO and prostacyclin have been reported to be effective treatment by clinicians, but tachyphylaxis to iNO therapy is a problem (communication via NZ COVID-19 Doctors Facebook Group from staff at Royal Free Hospital, UK). Inhaled NO therapy was also reported to be effective for hypoxaemia during the SARS coronavirus outbreak in 2002 [3], again suggesting a possible component of ventilation: perfusion mismatch or pulmonary hypertension in coronavirus associated pneumonia. The underlying mechanism for pulmonary hypertension is impaired pulmonary vascular function, particularly impaired function of the enzyme endothelial nitric oxide synthase (eNOS) and therefore lower local production of NO. Of note, significantly lower serum folate has also recently been reported in patients with severe COVID-19 infection [4].

Endothelial function and eNOS itself are both directly affected by folate supplementation. Folate affects eNOS function, both directly and by enhancing availability of its cofactor, tetra-hydro biopterin (BH_4) [5]. It may also enhance NO bioavailability via scavenging superoxide [6]. Endothelial function in the coronary circulation improves within hours of oral folate administration [7] and within minutes of intravenous 5-methyl-tetrahydrofolate, its active form [8]. In the systemic circulation, we have shown that a high dose of oral folic acid (5 mg) rapidly reverses endothelial dysfunction in children with type 1 diabetes [9], assessed using flow-mediated dilatation, a nitric oxide mediated process [10]. This effect occurred within two hours following administration and was sustained acutely for 4 h and for at least 8 weeks with on-going therapy with no adverse effects. Response to folic acid may however also be dependent on particular genetic polymorphisms in eNOS [11], with carriers of an insertion, which influences NO production, being more likely to respond to folic acid in our studies [11]. Importantly, folate also prevents tolerance to nitrates in the systemic circulation [12].

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Limited data suggest an effect of folic acid on the pulmonary vasculature via eNOS. In both human pulmonary artery endothelial cells and murine pulmonary arteries exposed to hypoxia, folic acid reverses uncoupling of eNOS and restores NO production [13]. Pulmonary hypertension also occurs in children with cobalamin-C deficiency [14,15] and total plasma homocyst(e)ine is elevated in individuals with primary pulmonary hypertension [16], supporting a role for folic acid metabolism in development of pulmonary hypertension.

Hypothesis

In combination, these data suggest high doses of folic acid may have a beneficial effect on pulmonary perfusion or the treatment of pulmonary hypertension, both directly and by enhancing the effectiveness of iNO or by preventing tachyphylaxis to iNO (via its enhancement of NO bioavailability and reduction in degradation), at least in some patients, with minimal risk of adverse consequences. Although folate could have an effect in a variety of situations in which pulmonary hypertension occurs, during the current COVID-19 out-break it may be of specific benefit in patients with hypoxaemia associated with severe pneumonia in whom iNO therapy is being considered. We hypothesise that in these patients, folic acid, 5–10 mg administered orally (or the equivalent dose, 50–100 mcg, of the active form 5-methyltetrahydrofolate intravenously, if the oral route is unavailable) will: 1) rapidly improve hypoxaemia due to pulmonary hypertension and 2) prevent tachyphylaxis to iNO therapy.

Testing these hypotheses could initially occur in a case series of patients affected by severe COVID-19 pneumonia in whom iNO is being considered. As the effect in the systemic circulation occurs within two hours [9], improvement in hypoxia would be expected over a similar time-frame in individuals, if it is effective. To assess an impact on tachyphylaxis to iNO, the effect of the addition of oral folate 5 mg daily to the length of time that iNO was required and dose requirements over time could be assessed. If there was any evidence of benefit from individual cases or a case series, then a formal randomised controlled trial over a short time period would establish effectiveness.

Being physicians fortunate enough to live in countries that have been less affected by severe COVID-19 disease, we are not in a position to test these hypotheses ourselves, but submit the idea to the medical community in case it does prove to have some benefit for some patients, as an adjunctive therapy with very low risk even when given for longer periods.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110142.

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