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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia

Esko Wiltshired, Alexia Sophie Peñae,d, Karen MacKenzie,e,f, Geoffrey Shawg,h, Jennifer Couperc,d

ABSTRACT

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 (BH4) [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].

* Corresponding author at: Department of Paediatrics and Child Health, University of Otago Wellington, PO Box 7343, Wellington South, New Zealand.
E-mail address: esko.wiltshire@otago.ac.nz (E. Wiltshire).

https://doi.org/10.1016/j.mehy.2020.110142
Received 13 July 2020; Accepted 23 July 2020
0306-9877/ © 2020 Elsevier Ltd. All rights reserved.
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 homocysteine 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.

Acknowledgement

This work in the systemic circulation, on which this hypothesis is based, was supported by the National Health and Medical Research Council Australia – Research Grant 519245.

Appendix A. Supplementary data

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

References

[1] Dunlap B, Weyer G. Am Fam Phys 2016;94:464–9.
[2] Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53(1):1801916.
[3] Chen L, Liu P, Gao H, Sun B, Chao D, Wang F, et al. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in beijing. Clin Infect Dis 2004;39(10):1531–5.
[4] Ietlman E, Wasserstrum Y, Segev A, Avak Y, Negru I, Cohen D, et al. Clinical characterization of 162 COVID-19 patients in Israel: preliminary report from a large tertiary center. Israel Med Assoc J 2020;22:271–4.
[5] Stroes ES, van Faassen EE, Yo M, Mantsaek P, Boer P, Govers R, et al. Folic acid reverses dysfunction of endothelial nitric oxide synthase. Circ Res 2000;86:1129–34.
[6] Staniewicz AE, Kenney WL. Role of folic acid in nitric oxide bioavailability and vascular endothelial function. Nutr Rev 2016;75(1):61–70.
[7] Douhi SN, McDowell IF, Moat SJ, Payne N, Durrant HJ, Lewis MJ, et al. Folic acid improves endothelial function in coronary artery disease via mechanisms largely independent of homocysteine lowering. Circulation 2002;105(1):22–6.
[8] Verhaar MC, Wever RM, Kastelein JJ, van Damm T, Koomans HA, Rabelink TJ. 5-methyltetrahydrofolate, the active form of folic acid, restores endothelial function in familial hypercholesterolemia. Circulation 1998;97(3):237–41.
[9] MacKenzie KE, Wiltshire EJ, Gent R, Hirte C, Pirotto L, Cooper JJ. Folate and vitamin B6 rapidly normalize endothelial dysfunction in children with type 1 diabetes mellitus. Pediatrics 2006;118(1):542–53.
[10] Joannides R, Hafefi WE, Linder I, Richard V, Bakkali EH, Thulillez C, et al. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 1995;91:1314–9.
[11] Wiltshire EJ, Peña AS, MacKenzie K, Bose-Sundernathan T, Gent R, Cooper JJ. A NOS3 polymorphism determines endothelial response to folate in children with type 1 diabetes or obesity. J Pediatr. 2015;166(2):319–25.e311.
[12] Gori T, Burstein JM, Ahmed S, Miner SES, Al-Hesayen A, Kelly S, et al. Folic acid prevents nitroglycerin-induced nitric oxide synthase dysfunction and nitrate tolerance. Circulation 2001;104(10):1119–23.
[13] Chalupa E, Kračun D, Kanchev I, Bertram K, Górlich A. Folic acid promotes recycling of tetrahydrobiopterin and protects against hypoxia-induced pulmonary hypertension by recoupling endothelial nitric oxide synthase. Antioxid Redox Signal 2015;23(14):1076–91.
[14] Iodice FG, Di Chiara L, Aiello C, Monti L, Cogo P, et al. Cobalamin C defect in children with isolated pulmonary hypertension. Pediatrics 2013;132(1):e248–51.
[15] Gündüz M, Ekici F, Özaydın E, Ceylaner S, Perez B. Reversible pulmonary arterial hypertension in cobalamin-dependent cobalamin C disease due to a novel mutation in the MMACHC gene. Eur J Pediatr 2014;173(12):1707–10.
[16] Arroliga AC, Sandur S, Jacobsen DW, Tewari S, Mustafa M, Mascha EJ, et al. Association between hyperhomocysteinemia and primary pulmonary hypertension. Respir Med 2003;97(7):825–9.