physical activity per se. It is uncertain how to measure psychological stress in the elderly retired population, and this could be a confounding factor that should be adjusted for in future studies.

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Cicletanine for the Treatment of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group I pulmonary hypertension) is characterized by elevated pulmonary arterial pressure leading to progressive dyspnea, right-sided heart failure, and ultimately death. The goal in treating PAH is to reduce pulmonary vascular resistance and pulmonary artery pressure as well as improve the functional status of the patient. The pathogenic hallmark of PAH is increased pulmonary vascular resistance, a result of vasoconstriction, vascular remodeling (abnormal proliferation of smooth muscle and sometimes other vascular tissue), and in situ thrombosis. An important root cause of this pathologic condition is endothelial dysfunction, ie, the uncoupling of endothelial nitric oxide synthetase (eNOS), which drives the decrease in the production of the endogenous vasodilator nitric oxide along with increases in the production of the reactive oxygen species peroxynitrite and superoxide.

Unfortunately, for many patients the current treatments used for PAH have limited efficacy and may not substantially alter the clinical course of the disease. This is probably, at least in part, because drugs currently approved for PAH (prostacyclins, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors) do not comprehensively address endothelial dysfunction itself but instead endeavor to counterbalance some subset of its downstream effects (ie, decreased prostacyclin production, increased endothelin production, and decreased nitric oxide and cyclic guanosine monophosphate production; Figure 1). We describe patient with progressive disease who was not responding to maximal conventional therapy and subsequently responded to treatment with cicletanine, an eNOS coupler currently used in Europe for systemic hypertension.

Report of a Case. A 33-year-old woman with progressive idiopathic PAH was admitted for progressive dyspnea on exertion and right heart failure. One year prior to admission, she was diagnosed as having idiopathic PAH (right ventricular pressure of 80/10 mm Hg) (right ventricular end-diastolic pressure of 33 mm Hg), pulmonary artery pressure of 72/33 mm Hg (main pulmonary artery pressure of 50 mm Hg), and pulmonary capillary wedge pressure of 8 mm Hg). She initially responded to treatment with intravenous treprostinil and sildenafil citrate, improving from WHO functional class IV to WHO functional class III. On admission, her blood pressure was 92/50 mm Hg; heart rate, 122/min; respiratory rate, 22/min; and oxygen saturation by pulse oximetry, 89% with 5-L/min nasal cannula oxygen. Findings from admission echocardiography and right-heart catheterization confirmed severe PAH and right ventricular dysfunction, with a mean pulmonary artery pressure of 55 mm Hg, right ventricular end-diastolic pressure of 18 mm Hg, and pulmonary capillary wedge pressure of 8 mm Hg (mixed venous oxygen saturation of 57%). On the basis of her symptoms, the patient was categorized as WHO functional class IV. She had been receiving pulmonary vasodilator therapy with high-dose intravenous treprostinil and tadalafil, in addition to furosemide (80 mg twice daily) and spironolactone (30 mg twice daily). While in the intensive care unit, she began therapy with tadalafil (20 mg daily). Blood pressure increased to 122/65 mm Hg with a heart rate of 105/min and an oxygen saturation of 96% with 4-L/min nasal cannula oxygen. On day 6 of hospitalization, her blood pressure was 130/78 mm Hg; heart rate, 99/min; respiratory rate, 15/min; and oxygen saturation 99% with 3-L/min nasal cannula oxygen. On day 10, her symptoms improved and the patient was discharged home on tadalafil and diuretics and was able to walk further than she could on the day of admission.

Figure 1. The pathophysiologic mechanisms of pulmonary arterial hypertension. Endothelial dysfunction (endothelial nitric oxide synthetase [eNOS] uncoupling) is the common, upstream driver of vasoconstriction and vascular remodeling. Currently approved treatments (endothelin receptor antagonists [ETRAs], phosphodiesterase 5 [PDE5] inhibitors, prostacyclins) act downstream from eNOS uncoupling (via [1] decrease of endothelin production, [2] decrease of cyclic guanosine monophosphate [cGMP] hydrolysis, and [3] increase of exogenous prostacyclin production). ET1 indicates endothelin-1; NO, nitric oxide; NO3–; nitrate; O2–; oxygen; and PGI2, prostacyclin.
nitric oxide synthase isoenzymes that convert L-arginine to L-citrulline, resulting in the production of nitric oxide generated by eNOS regulates blood pressure, platelet aggregation, leukocyte adherence, and vascular smooth muscle cell mitogenesis. When eNOS is uncoupled (ie, not dimerized), production of nitric oxide is decreased and production of the reactive oxygen species peroxynitrite and superoxide is increased; vascular remodeling may also ensue. Uncoupling of eNOS is referred to as endothelial dysfunction. Endothelial dysfunction is associated with the pathogenesis of a variety of forms of pulmonary hypertension, as well as several other disorders, including heart failure and systemic hypertension.

An increasing amount of evidence supports a potential role for cicletanine in the treatment of disorders associated with endothelial dysfunction, including PAH. Several preclinical studies have supported the view that cicletanine acts as a coupler of eNOS by acutely activating eNOS by physical stimuli such as hemodynamic shear stress and by hypoxia. Agonists of diverse G protein–coupled cell surface receptors increase the production of nitric oxide, as attempts to discontinue treatment with the inhaled nitric oxide resulted in a significant, symptomatic decrease in cardiac output. She had marked volume overload, and her functional status remained unchanged (WHO class IV). The patient was not interested in lung transplantation; therefore, compassionate treatment with cicletanine was begun at 50 mg/d and was increased to a dose of 150 mg/d over a 3-day period. Immediately prior to the initiation of cicletanine therapy, she had a 6-minute walk distance of 30 m while breathing nitric oxide at 80 parts per million. Over the subsequent week she was weaned off nitric oxide and was transferred to the cardiac step-down unit. On the day of transfer, her central venous oxygen saturation was 71%. A maintenance regimen of treprostinil (143 ng/kg/min), tadalafil (40 mg/d), sitaxsentan (100 mg/d), furosemide (80 mg twice daily), spironolactone (50 mg twice daily), and cicletanine (150 mg/d) was prescribed, and the patient (now classified as WHO class III) was discharged home. Figure 2 details the patient’s progress. After 3 months of cicletanine therapy, her oxygen saturation was 98% at rest while breathing room air; her heart rate had decreased from 135/min to 105/min, her blood pressure had improved 120/60 mm Hg; her weight had decreased from 75 kg to 60 kg; and her 6-minute walk distance had increased from 30 m to 446 m. Her serum N-terminal pro-brain natriuretic peptide level had decreased from 4409 pg/mL to 1859 pg/mL (age corrected normal range, 0-450 pg/mL). She no longer required high doses of diuretics, and furosemide therapy was decreased from 80 mg twice per day to 40 mg once per day. Sitaxsentan therapy was discontinued, and ambrisentan therapy (5 mg/d) was begun. She required no other changes in her maintenance vasodilator therapy. After 6 months of therapy her medical regimen remained unchanged. Her 6-minute walking distance was stable, as were her vital signs. Her N-terminal pro-brain natriuretic peptide level had decreased further to 1525 pg/mL. Her functional class had steadily improved from WHO class II. Unfortunately, 3 weeks after her 6-month follow-up visit, she visited our hospital for septic shock due to a staphylococcal Hickman catheter infection. The catheter was being used for continuous delivery of treprostinil. She did not recover and died of cardiac arrest.

Comment. To our knowledge, this is the first documented case of administration of cicletanine, an eNOS coupler, to an adult patient with PAH. The endothelial isoform of nitric oxide synthase, eNOS, is one of 3 nitric oxide synthase isoenzymes that convert L-arginine to L-citrulline, resulting in the production of the key signaling molecule nitric oxide. Agonists of diverse G protein–coupled cell surface receptors acutely activate eNOS by physical stimuli such as hemodynamic shear stress and by hypoxia. Nitric oxide generated by eNOS regulates blood pressure, platelet aggregation, leukocyte adherence, and vascular smooth muscle cell mitogenesis. When eNOS is uncoupled (ie, not dimerized), production of nitric oxide is decreased and production of the reactive oxygen species peroxynitrite and superoxide is increased; vascular remodeling may also ensue. Uncoupling of eNOS is referred to as endothelial dysfunction. Endothelial dysfunction is associated with the pathogenesis of a variety of forms of pulmonary hypertension, as well as several other disorders, including heart failure and systemic hypertension.

An increasing amount of evidence supports a potential role for cicletanine in the treatment of disorders associated with endothelial dysfunction, including PAH. Several preclinical studies have supported the view that cicletanine acts as a coupler of eNOS by showing increases in nitric oxide production and decreases in the production of peroxynitrite or decreases in superoxide (in some cases all 3 in the same study). There is an appreciable number of clinical studies of cicletanine showing favorable effects in endothelial dysfunction–associated disorders, in particular hypertension. Of note is a published study showing improvement in pulmonary hemodynamics among patients taking cicletanine for pulmonary hypertension associated with chronic hypoxia (WHO group III pulmonary hypertension) due to chronic obstructive pulmonary disease. In addition, there was a favorable study of cicletanine in pulmonary hypertension associated with left-sided heart failure (WHO group II pulmonary hypertension) in this case, the patients were on a heart transplant waiting list and improved on average 0.9 New York Heart Associa-

Figure 2. Time course of clinical change in 6-minute walk distance (circles) and modified Borg dyspnea index (squares) (A) and pro–N-terminal pro-brain natriuretic peptide (NT-proBNP) (triangles) (B). Time point zero represents the start of cicletanine therapy.
tion functional status points from baseline. Cicletanine is the first agent of which we are aware of having favorable clinical signals in all 3 of these types (WHO groups I, II, and III) of pulmonary hypertension. Furthermore, there are several animal studies showing favorable cardiac effects, including reversal of cardiac hypertrophy and reduction in extent of ischemia-induced myocardial infarction.\textsuperscript{17,19}

The greater than 50\% reduction in N-terminal pro-brain natriuretic peptide level in our patient, along with her marked clinical improvement as evidenced by a decrease in supplemental oxygen requirements and increased walking distance, is consistent with the hypothesis that cicletanine had a beneficial effect on both pulmonary vascular resistance and right ventricular function in this patient with severe idiopathic PAH. This in turn is consistent with the view that cicletanine directly treats endothelial dysfunction, which is thought to be a principal driver both in pulmonary hypertension and cardiac failure.

While we believe cicletanine played a pivotal role in the observed improvement in this patient, an obvious limitation to the interpretation of our findings was the combination of multiple interventions in close succession. This limits our ability to separate clearly the effects of the different interventions.

In conclusion, cicletanine, an eNOS coupler, may represent a novel therapy to target both vascular remodeling and right ventricular dysfunction in PAH. The initial adult PAH case reported herein gives hope that cicletanine could represent a new, important class of drugs to treat pulmonary hypertension. Further study of this agent in PAH is warranted.

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COMMENTS AND OPINIONS

Consideration of Extrarenal Creatinine Clearance in the Measurement of Renal Function After Bowel Endoscopy

In a large retrospective study, Khurana and colleagues\textsuperscript{1} report that oral sodium phosphate solution preparation is associated with a decline in glomerular filtration rate in elderly patients relative to controls following colonoscopy. Glomerular filtration rate was estimated based on serum creatinine levels. Recommendations were made to limit the use of oral sodium phosphate solution in patients undergoing colonoscopy because of a concern for decreased renal function in at-risk patients.

We propose that methods of glomerular filtration rate calculation based on values for serum creatinine overlook the potential impact of cleansing preparations on bowel flora involved in extrarenal creatinine clearance. Creatinine is normally secreted into the digestive tract. However, bacteria expressing creatininas enzymes may metabolize this secreted creatinine, resulting in an extrarenal “clearance.” Such bacteria have been shown to be induced signifi-