An unexpected therapeutic effect of isosorbide dinitrate on challenging chronic tracheobronchitis

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Summary

Two patients have suffered from chronic tracheobronchitis for twenty years and were treated by traditional therapy. However, chronic tracheobronchitis has never been completely cured. They develop lasting drastic morning coughing because of throat abnormal sensation caused by sticky phlegm. The chronic tracheobronchitis was obviously relieved, in most conditions was totally disappeared, since the third month they regularly took isosorbide dinitrate (ISDN) for angina pectoris. This unexpected effect of ISDN is remarkable, and given the smooth muscle relaxation mechanism, this may provide a potential therapeutic idea that takes advantage of similar drugs both for angina pectoris and chronic tracheobronchitis.

Background: Chronic tracheobronchitis involves nonspecific and prolonged inflammation of the tracheal mucosa and surrounding tissues, and is caused by infectious or non-infectious factors. Therapeutic strategies include infection control, expelling phlegm to arrest coughing, spasmolysis, and asthma calming. However, in most cases, these treatments only temporarily relieve the symptoms, and an effective therapeutic is still needed ([1](#)).

Objective: To report an unexpected but impressive therapeutic effect of isosorbide dinitrate (ISDN), a nitrate that dilates blood vessels ([2](#)), on a challenging, 20-year-old case of chronic tracheobronchitis.

Results: A 64-year-old male patient (patient A) had suffered from challenging chronic tracheobronchitis for nearly 20 years. He developed the classic symptoms,

such as extremely drastic coughing lasting for more than 30 minutes every morning right after getting up to struggle to clean out some sticky phlegm. The morning coughing was mainly caused by the abnormal sensation of sticky phlegm, but not trachea itching. He was treated with aminophylline, ambroxol, and antibiotics such as amoxicillin occasionally when the tracheobronchitis symptoms were increased by infection or cold. However, the chronic tracheobronchitis was never completely cured, and the drastic morning coughing continued daily. About two years ago, he began to take ISDN every morning and evening (5 mg/time) to treat angina pectoris, another disease that had emerged at that time. We noticed that his morning coughing was obviously alleviated, and in most conditions, it almost totally disappeared. Moreover, the extremely sticky phlegm turned to dense phlegm with a dark yellow color and low viscosity, making it much easier to be expectorated, and a possible reason for the reduction of the lasting and struggling morning coughing. According to the patient's narration, he noticed remarkable relief of tracheobronchitis symptoms by himself after about 2 months of continuous treatment of ISDN.

Patient B, 79 years old, is the elder full brother of Patient A and had a very similar medical and treatment history, with ISDN treatment initiated nearly twenty years ago. Similar to Patient A, his morning coughing had similarly disappeared following initiation of ISDN treatment, and the tracheobronchitis has remained suppressed for about twenty years. However, patient B's exact medical and drug history was not accurately remembered currently because of the long period.

Both patients also suffered from hypertension, and they had been taking captopril and other drugs (irbesartan or nifedipine) for treatment. However, the chronic tracheobronchitis symptoms were unaffected until they began taking ISDN for angina pectoris. They also had smoked since they were young, and they kept the smoking habit until now, which led to mild obstructive ventilation dysfunction (Figure 1). However, according to the clinician's diagnosis, the mild obstructive ventilation dysfunction did not result in chronic tracheobronchitis relief. Thus, the relief of chronic tracheobronchitis was not related to their smoking habit. In conclusion, we carefully investigated their disease and treatment history, and found that, according to a temporal causal analysis, the impressive relief of challenging chronic tracheobronchitis was strongly related to the continuous ISDN treatment instead of other drugs (Table 1 & Figure 2).

Discussion: ISDN is available as a generic medication on the World Health Organization's List of Essential Medicines and is rated as one of the most effective and safe medicines needed in the health care system (3, 4). Common side effects caused by ISDN include lightheadedness with standing, blurred vision, headache, and low blood pressure. Similar to other nitrates or organic nitrates, ISDN turns to nitric oxide to activate the enzyme guanylate cyclase. This process stimulates the dephosphorylation of the myosin light chain of smooth muscle fibers and induces smooth muscle cell relaxation and vasodilation (4). A similar mechanism may also occur in the tracheal smooth muscle cells and may explain the effect of ISDN on challenging chronic tracheobronchitis. Given that the mechanism of ISDN is smooth muscle relaxation, a further systematic study may identify a potential therapeutic

target that takes advantage of similar drugs for simultaneously treating angina pectoris and chronic tracheobronchitis.

This was a totally unexpected but impressive effect of ISDN, based on the significant relief, even disappearance, of struggling morning coughing. Additional scientific pre-clinical and clinical trials are still needed to systematically study the effect of ISDN on challenging chronic tracheobronchitis. Moreover, because both challenging chronic tracheobronchitis and angina pectoris are common diseases for the middle-aged and elderly patients, special attention should be paid to analyze the different curative effects of ISDN on patients suffering from the two diseases or only chronic tracheobronchitis. A systematic study will also eliminate a potential hereditary dependence, which could be a factor in our study, since the two patients are full brothers. Our study identifies ISDN as a potential therapeutic for chronic tracheobronchitis, and is especially warranted for patients who suffer from both challenging chronic tracheobronchitis and angina pectoris at the same time, where ISDN may have the effect of killing two birds with one stone.

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References

1. Silverman M, Povitz M, Sontrop JM, Li L, Richard L, Cejic S, et al. Antibiotic prescribing for nonbacterial acute upper respiratory infections in elderly persons. *Annals of internal medicine*. 2017;166(11):765-74.
2. Cole RT, Kalogeropoulos AP, Georgiopoulou VV, Gheorghiade M, Quyyumi A, Yancy C, et al. Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and future directions. *Circulation*. 2011;123(21):2414-22.
3. Organization WH. 19th WHO model list of essential medicines. World Health Organization, Geneva, Switzerland. 2015.
4. Rang HP, Ritter JM, Flower RJ, Henderson G. Rang & Dale's Pharmacology E-Book: Elsevier Health Sciences; 2014.

Figure 1. Pulmonary function test of patient A. A mild obstructive ventilation dysfunction was diagnosed according to the pulmonary function testing data.

Figure 2. Medical and drug history diagram of patient A. Temporal causal analysis shows a close causal relationship between the relief of challenging chronic tracheobronchitis and isosorbide dinitrate (ISDN) treatment.

Table 1. Medical and drug history of patients A and B.

	Date of birth	Medical History	Drug Therapy History	Risk Factors
Patient A	June 1955	Chronic	Captopril (48-59 years old, 2003-2015)	Smoking
	64 years old Male	Tracheobronchitis Angina Pectoris Hypertension Hyperlipemia	Amlodipine Besylate (Since 60 years old in 2015) Irbesartan (Since 60 years old in 2015) Aminophylline and Ambroxol (occasionally) Antibiotics (occasionally) ISDN (Since 62 years old in 2017) Simvastatin (Since 63 years old in 2018)	(Since 14 years old in 1969)
Patient B	Nov. 1940	Chronic	Captopril (Since about 50 years old in 1990)	Smoking
	79 years old Male	Tracheobronchitis Angina Pectoris Hypertension	Nifedipine (Since about 70 years old in 2010) Antibiotics (occasionally) ISDN (Since about 60 years old in 2000)	(Since about 25 years old in 1965)

ISDN: isosorbide dinitrate.