Communication

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Oral high-dose acetylcysteine: Effective against the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)?

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SUMMARY The Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a high rate of transmission and it exhibits immune escape characteristics. N-acetyl-L-cysteine (NAC) is a precursor of reduced glutathione (GSH), which can enter cells to play an antioxidant role, so it is better than glutathione. Patients tolerate NAC well, and adverse reactions are rare and mild, so this type of drug with multiple actions is considered to be a mucolytic agent as well as a drug for the prevention/treatment of various diseases, including COVID-19. Previous studies indicated that the clinical effectiveness of NAC is dose-dependent. Low-dose NAC (0.2 g tid for adults) is a mucolytic expectorant, high-dose NAC (0.6 g bid or tid) has expectorant action as well as antioxidant action, and extreme-dose NAC (300 mg/kg.d) is used for detoxification in cases of an acetaminophen overdose. Presumably, orally administered high-dose NAC (0.6 g tid for adults and 10 mg/kg tid for children) could be used as an adjuvant to treat an Omicron infection. It should reduce the time to negative conversion and prevent severe COVID-19, reducing the duration of hospitalization and increasing the bed turnover rate.

Keywords Omicron, N-acetyl-L-cysteine (NAC), high-dose, oral, effectiveness

In November 24, 2021, a highly variable variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) named "Omicron (B.1.1.529)" by the World Health Organization (WHO) was discovered in South Africa. Omicron has a high rate of transmission and it exhibits immune escape characteristics. Omicron has a higher rate of infection than the Delta variant, but fortunately Omicron's symptoms are mild, and the rate of hospitalization, the rate of severe disease, and its mortality rate are relatively low (*1*). However, serious cases of Omicron have been reported. Italy reported the first case of severe acute respiratory syndrome caused by Omicron in November 2021 (*2*). As of March 30, 2022, Shenzhen's Third People's Hospital, the only hospital designated to treat COVID-19 in Shenzhen, China, has admitted about 2,600 patients with COVID-19, including about 1,800 with an Omicron infection. Elderly patients and patients with comorbidities, including diabetes, cardiovascular disease, and compromised immunity, are known to be at risk of becoming severely or critically ill. In addition, 20% of patients infected with Omicron were children, who accounted for a very low proportion of patients infected with the Delta variant. Fever and gastrointestinal symptoms in children were more severe than those in adults, and the time to negative conversion was longer. Therefore, the following questions need to be considered: 1. How can patients test negative for the nucleic acids of SARS-CoV-2 as soon as possible and meet the discharge criteria; 2. How can mild cases be prevented from developing into severe or critical cases? (This especially applies to the elderly and children).

COVID-19 can lead to complications such as pneumonia, acute respiratory distress syndrome, cardiovascular disease, and multiple organ failure (possibly due to a cytokine storm), a systemic inflammatory response, and an immune system attack. In addition, excessive oxidative stress is one factor that contributes to the pathophysiology of COVID-19 (*3*). N-acetyl-L-cysteine (NAC) is a precursor of reduced glutathione (GSH), which can enter cells to play an antioxidant role, so it is better than glutathione. Patients tolerate NAC well, and adverse reactions are rare and mild, so this type of drug with multiple actions is considered to be a mucolytic agent as well as a drug for the prevention/treatment of various diseases, including the consumption of glutathione supplements (glutathione

is an antioxidant) in order to combat oxidative stress. Therefore, NAC is a treatment or adjuvant therapy for the following diseases: infectious diseases such as influenza and acquired immunodeficiency syndrome, digestive system diseases such as Crohn's disease and ulcerative colitis, nervous system diseases such as schizophrenia, bipolar disorder, obsessive compulsive disorder, Parkinson's disease, multiple sclerosis, peripheral neuropathy, and stroke (*4*).

Previous studies have reported that NAC inhibits the replication of influenza viruses such as H5N1, it reduces the release of inflammatory factors, it reduces oxidative stress and oxidative damage caused by inflammatory mediators, and it reduces damage to the human body (*5,6*). Studies have also confirmed that NAC can be used as an adjuvant therapy for idiopathic pulmonary fibrosis and pulmonary fibrosis after COVID-19 (*7,8*). A clinical trial indicated that NAC supplements can quickly alleviate a GSH deficiency, antioxidant stress, and oxidative damage in patients with COVID-19 (*9*). Therefore, NAC has recently been proposed as a potential adjuvant therapy for COVID-19 (*10,11*). The mechanisms of NAC therapy for COVID-19 include: 1. inhibiting the envelope (E) protein and thorn (s) protein of the virus and reducing its binding to angiotensin II receptors (AT2R); 2. inhibiting angiotensin-converting enzyme (ACE); 3. inducing the synthesis of endogenous GSH so as to enhance antioxidation and reduce intracellular protein glycosylation; and 4. inhibiting the production of proinflammatory mediators and cytokines (*12*). In addition, high-dose intravenous NAC is reported to play a key role in the treatment of severe cases of COVID-19 (*3,13,14*).

Further research has indicated that the clinical effectiveness of NAC is dose-dependent. Low-dose NAC (0.2 g tid for adults) is a mucolytic expectorant, high-dose NAC (0.6 g bid or tid) has expectorant action as well as antioxidant action, and extreme-dose NAC (300 mg/kg.d) is used for detoxification in cases of an acetaminophen overdose. For patients suffering from an acetaminophen overdose, the initial intravenous dose of NAC is 300 mg/kg over 21 hours, and then 100 mg/kg is infused for more than 16 hours until the level of acetaminophen is less than 20 μg/mL and aspartate aminotransferase (AST) and alanine transaminase (ALT) levels tend to decrease (*15*). For patients with idiopathic pulmonary fibrosis, the NAC dose is 1,800 mg/d (600 mg, tid) orally for more than 1 year, and no adverse reactions were noted (*7*). Twelve patients with chronic obstructive pulmonary disease (COPD) were randomly treated with NAC 1,800 mg per day for 3 months; the treatment was effective without causing adverse reactions (*16*). That said, a study has suggested that whether low-dose NAC (less than or equal to 600 mg per day) is effective in treating COPD is uncertain (*17*). Clinical experiments have indicated that low concentrations of NAC (< 1 μM) in the blood cannot regulate the imbalance of bronchial oxidation, that high concentrations of NAC (2,300 μM) can inhibit the airway inflammatory response caused by nocturnal lipopolysaccharide (LPS) stimulation, and that extreme concentrations of NAC (21 μM) can reduce the release of IL-6 induced by LPS, indicating that high concentrations of NAC can alleviate oxidative damage (*18*). Lai *et al*. confirmed that oral high-dose NAC (1,200 mg, bid) can rapidly increase the level of glutathione in lymphocytes of patients with systemic lupus erythematosus with chronic inflammation, while low-dose NAC (600 mg, bid) cannot achieve this effect (*19*). There is little literature on the dosage for children. The dosage of NAC for treating β-thalassemia in children is 10 mg/kg.d (maximum dose of 600 mg) orally (*20*). Intravenous NAC was used to treat an acetaminophen overdose in children at a dose of 300 mg/kg.d, and the dose per kilogram of body weight of children is the same as that of adults (*21,22*).

NAC can be taken orally, intravenously, or atomized. Numerous studies have reported that oral NAC has the same effectiveness as an injection (*23-26*). NAC is well-tolerated. Compared to an injection, oral administration causes fewer adverse reactions. In most clinical trials, adverse reactions to NAC did not differ significantly from those to a placebo. The most common adverse reaction is mild gastrointestinal symptoms; adverse reactions are uncommon when the dose is less than 2.5 g/day (*27*).

Based on the findings above, orally administered high-dose NAC (0.6 g tid for adults and 10 mg/kg tid for children) could be used as an adjuvant instead of a low-dose expectorant (0.2 g tid for adults and 10 mg/kg qd for children) to treat an Omicron infection. It should reduce the time to negative conversion and prevent severe COVID-19, reducing the duration of hospitalization and increasing the bed turnover rate. The grounds for that contention can be summarized as follows: 1. NAC has been proven to have antiviral action in patients with influenza and adjuvant action in a variety of diseases; 2. Compared to an injection, oral administration is more convenient, safer, and causes fewer adverse reactions; 3. Low doses are only used as an expectorant and NAC's effectiveness as an adjuvant therapy for COVID-19 is uncertain, but only high doses have antioxidant, anti-inflammatory, and antiviral actions. Moreover, high doses of NAC also have expectorant action; and 4. Even if a high dose of NAC, such as 300 mg/kg.d, is injected, adverse reactions are rare and the drug is well-tolerated.

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