



# Re-recognizing bromhexine hydrochloride: pharmaceutical properties and its possible role in treating pediatric COVID-19

Qibo Fu<sup>1</sup> · Xiao Zheng<sup>2</sup> · Yunlian Zhou<sup>3</sup> · Lanfang Tang<sup>3</sup> · Zhimin Chen<sup>3</sup> · Shaoqing Ni<sup>4</sup> 

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The outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-coronavirus 2 (SARS-CoV-2) has become a pandemic and constitutes a global health emergency [1]. The number of infected children is increasing, with reports of children's deaths [2–6]. As with adults, no effective anti-COVID-19 therapy has been found yet for children [7–10].

Researchers from Germany recently provided evidence that the transmembrane protease serine 2 (TMPRSS2) plays a key role in SARS-CoV-2 binding to the host cell receptor, thereby achieving viral invasion and infection [11]. Other studies also suggest that TMPRSS2 is a drug target for treating COVID-19, and bromhexine was found to be a strong inhibitor of TMPRSS2 [12–14]. Bromhexine hydrochloride is approved in many countries as a commonly used over-the-counter (OTC) expectorant for both adults and children and has been marketed since 1963 [15, 16]. It is characterized by low side effects and relatively low cost [17]. Considering all these characteristics, bromhexine hydrochloride could be an ideal candidate as a potential COVID-19 treatment [17–19].

As far as safety is concerned, the incidence of adverse reactions to bromhexine hydrochloride has been similar in children and adults. Though unlikely, if there are signs or

symptoms of skin reactions or allergic reactions, patients should seek medical advice and discontinue bromhexine hydrochloride immediately [15]. It should be used with caution in the presence of obstructed bronchial motor function or large amounts of secretions [15]. Also, it is not recommended for use in children under 2 years of age owing to the risk of life-threatening side effects [20].

According to the results of cell experiments, the half maximal inhibitory concentration (IC<sub>50</sub>) of bromhexine hydrochloride on TMPRSS2 protease is 0.75 μM, and the target cell concentration is about 308.62 ng/mL [14]. The pharmacokinetic data for oral bromhexine hydrochloride show that the adult maximum blood concentration (C<sub>max</sub>) with oral administration of 8 mg bromhexine hydrochloride is 22.50 ± 7.50 μg/L [21], and the concentration in the parenchymal tissue of the lung is 54–132.75 ng/mL, far less than the concentration of target cells [22]. Because the new pharmacokinetic parameters of bromhexine hydrochloride are proportional to an oral dose of 8–32 mg [21], the pulmonary concentration with 32 mg of the drug would be 216–531 ng/mL (median 373.5 ng/mL), which could achieve the target cell concentration to inhibit TMPRSS2. In adults, Yong et al. suggested an oral dose of bromhexine hydrochloride up to 96 mg per day in clinical practice [23] to maximize the drug concentration in blood. We did not find reports of pediatric use experiences [24].

As of June 12, 2020, six clinical trials have been registered to explore the therapeutic potential of oral bromhexine hydrochloride in patients with COVID-19. The only clinical trial in children was registered by our group [25]. The use of new therapeutic methods in children should be undertaken very cautiously, because the pathogenesis of COVID-19 in children is still not clear. After comprehensive consideration of age, pharmacokinetics and safety, we propose initially studying the use of bromhexine hydrochloride at the maximum dosage recommended by drug labels in pediatric patients with suspected and mild cases of COVID-19. The oral dose will depend on age as follows: 12 mg, 24 mg and 48 mg daily in three divided doses for ages 2–5 (weight < 50 kg), 6–13

✉ Zhimin Chen  
zmchen@zju.edu.cn

✉ Shaoqing Ni  
chqcp@zju.edu.cn

<sup>1</sup> National Clinical Research Center for Child Health, National Children's Regional Medical Center, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China

<sup>2</sup> State Key Laboratory of Natural Medicines, College of Pharmacy, China Pharmaceutical University, Nanjing 210009, China

<sup>3</sup> Pulmonary Department, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China

<sup>4</sup> National Clinical Trial Institute, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China

(weight  $\geq 50$  kg) and 14–18, respectively. However, we have not recruited patients because very few children have been diagnosed with COVID-19 in China thus far.

We propose that the use of bromhexine hydrochloride in the treatment of pediatric COVID-19 be studied in clinical research and clinical practice to fight against the spread of COVID-19 throughout the world.

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## Compliance with ethical standards

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