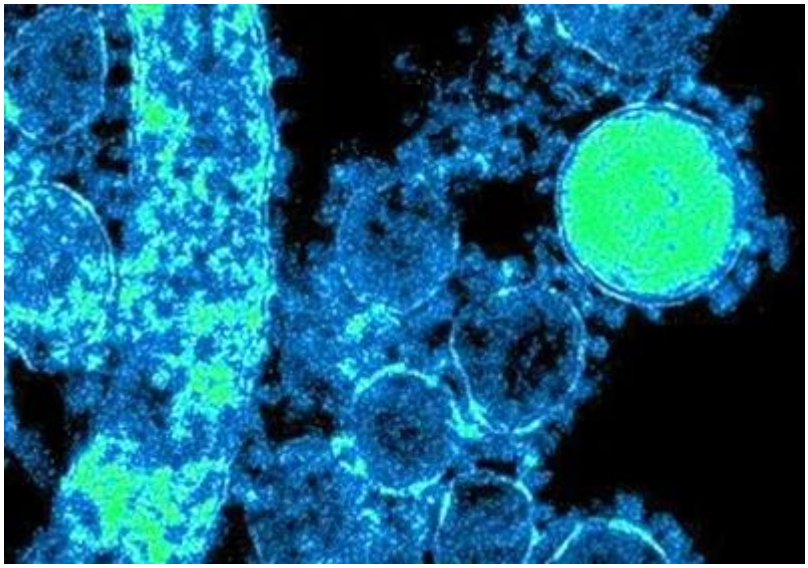
Probenecid is a uricosuric agent that was first approved in 1951 for the treatment of gout but was later found to have potent, broad-spectrum antiviral activity against several respiratory viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this randomized, placebo-controlled, Phase 2 study, the authors from the United States and India investigated the antiviral effect of probenecid and its efficacy in symptomatic, non-hospitalized patients diagnosed with symptomatic, mild-to-moderate COVID-19.

Previous studies on probenecid's antiviral activity have revealed that probenecid is a prototypic inhibitor of the organic anion transporter-3 gene (OAT3), an important host gene required for viral replication. *In vitro,* probenecid showed a potent inhibitory effect against several influenza A strains and *in vivo* reduced the lung viral titers in a mouse model of infection. Recent studies have shown that probenecid, administered prophylactically or after the infection, can potently inhibit SARS-CoV-2 and reduce the lung viral titers in a Syrian hamster model of SARS-CoV-2 infection. The authors emphasize that probenecid inhibits c-Jun N-terminal kinase (JNK) phosphorylation and regulates hepatocyte nuclear factor -4 (hfn-4) expression, which is involved in OAT3 gene expression. JNK signaling leads to a pro-viral state, whereas probenecid treatment inhibits JNK signaling, favoring an anti-viral state. Also, probenecid inhibits the generation of reactive oxygen species by inhibiting the COX-2 and JNK pathways, and it reduces the secretion of interleukin (IL)-1b dependent on NLRP3 inflammasome. This indicates that its function is dual, encompassing both antiviral and anti-inflammatory effects.



About the study

This phase 2, dose-range finding, randomized, single-blind, and placebo-controlled study evaluated the antiviral activity, clinical efficacy, and safety of orally administered probenecid in non-hospitalized, symptomatic patients with SARS-CoV-2 infection confirmed by polymerase chain reaction. Patients were randomly assigned in a 1:1:1 ratio to receive either 500 mg of probenecid, 1000 mg of probenecid, or a matching placebo every 12 hours for five days. Patients were blinded to study drug assignments, while study personnel were unblinded.

The COVID-19 symptoms were assessed at the beginning, and on days 3, 5, 10, 15, and 28. The vital signs assessments, i.e., body temperature, blood pressure, oxygen saturation, respiratory rate, and heart rate, were established following the WHO clinical progression scale.

Most patients were vaccinated with at least one dose of either Covishield or Covaxin. Co-morbidities were uncommon, with hypertension and diabetes mellitus being reported in less than 25% of patients. Key exclusion criteria were severe COVID-19 (either outpatient or hospitalized) or long COVID-19 syndrome. The primary endpoint in this study was the time to clearance of viral RNA in nasopharyngeal swabs.

Results

The study included 75 patients, with symptomatic, mild, or moderate COVID-19, aged 18-65

years. Every group involved 25 patients.

The results showed that the time to clearance of viral RNA from nasopharyngeal swabs was significantly shorter for the probenecid 1000 mg group *versus* placebo (7 days vs. 11 days) and for the probenecid 500 mg group *versus* placebo (9 days vs. 11 days). All patients receiving 1000 mg of probenecid cleared the virus by day 10, while patients treated with 500 mg of probenecid and those in the placebo-treated group cleared the virus by day 12.

All patients who had symptoms at baseline reported symptoms on days 3 and 5. At day 10, a greater proportion of patients who received probenecid 1000 mg reported complete resolution of symptoms compared to the placebo group (68% *vs.* 20%), and of patients who received probenecid 500 mg compared to placebo (56% vs. 20%). Between the two probenecid doses, there was no difference in symptom resolution. All patients who received probenecid 1000 mg had a complete resolution of symptoms by day 15, while patients treated with 500 mg or placebo reported a complete resolution by day 18.

All patients completed the study, without hospitalizations or deaths. Probenecid was generally safe and well tolerated, with only mild adverse events reported. The most frequently reported adverse events were gastrointestinal, including nausea and vomiting reported in 8% (2/25) of patients who received probenecid 1000 mg.

Conclusion

This study demonstrated a dose-dependent antiviral effect of probenecid in patients with symptomatic, mild-to-moderate COVID-19, with a significant, dose-dependent reduction in the time to clearance of viral RNA in nasopharyngeal swabs. Treatment with probenecid was generally safe and well tolerated. The authors concluded that future studies should explore the efficacy of probenecid in patients with severe COVID-19 and patients over 65 years.

This study was published in Viruses.

Journal Reference

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