Antiviral activity against SARS-CoV-2

Molecule tested: Nabumetone

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Introduction

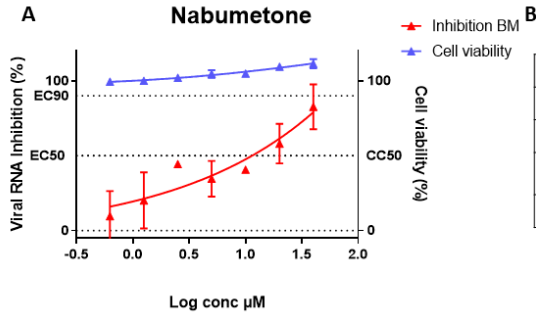
In response to the recent emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, the Unité des Virus Émergents performed preclinical evaluation of drug candidates against SARS-COV-2. **This interim report has not been peer-reviewed.** The data of this report are available upon request.

The molecule tested here is Nabumetone: a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities which is used in therapy of chronic arthritis.

In vitro evaluation of efficacy of Nabumetone

Nabumetone was identified as a potential hit by an antiviral screen based on the SARS-CoV-2 cytopathic effect inhibition (Touret et al., 2020).

Then, the antiviral activity was further characterized from 40 µM to 0.6 µM in Vero-E6 cells using a viral RNA yield reduction assay as previously described (Touret et al., 2019, Touret et al., 2020). Dose-response curves are presented in figure 1A. Nabumetone showed half maximal effective concentration (EC50) and 90% effective concentration (EC90) of 11.41µM and 57.37µM respectively, without any cytotoxicity at these concentrations (Figure 1B). As Nabumetone was found to be effective against SARS-CoV-2 with a selectivity index (SI) of 3.5 its antiviral activity was evaluated *in vivo*.



B

µM	Nabumetone
EC50	11,41
EC90	57,37
CC50	>40
SI	>3,5

Figure 1: *In vitro* evaluation of Nabumetone in VeroE6 cells. A: Dose response and cytotoxicity evaluation. B Nabumetone interpolated antiviral activity values. All assay were performed as previously described (Touret et al., 2020).

In vivo evaluation of efficacy of Nabumetone

Experiments were approved by the local ethical committee (C2EA—14) and French authorities (APAFIS#23975). Four-week-old female Syrian hamsters were intranasally infected with 10^4 TCID50 of the BavPat1 SARS-CoV2 strain as described previously (Driouich et al., 2020). To assess the efficacy of nabumetone, a group of 6 hamsters received the drug, orally, two times a day (BID). We used one dose of 590 mg/kg/day. Treatment was initiated at day of infection, ended at 2 day post infection (dpi) and animals were sacrificed at 3 dpi. A control group of 6 infected/untreated animals received, orally, 0.9% Sodium Chloride solution. Viral replication was measured in lungs (viral RNA yields) and in plasma (viral RNA yields).

Results showed no significant reduction of viral replication in lungs and plasma compared to control group (**Figure 2**).

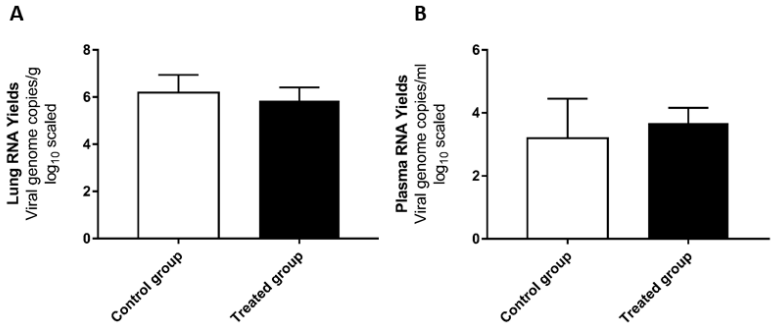


Figure 2: Viral replication in lungs (A) and in plasma (B). Lung and plasma viral load were measured using a viral RNA yields RT-qPCR assay as previously described (Driouich et al., 2020).

Conclusion

Nabumetone was found to inhibit SARS-CoV-2 replication *in vitro* using Vero-E6 cells. However, results obtained using a hamster model suggest that this molecule is a poor inhibitor of SARS-CoV-2 replication *in vivo.*

References

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