

# OTOTOXIC EFFECTS OF DRUGS USED IN COVID-19 THERAPIES IN COMPARISON TO WELL-KNOWN OTOTOXIC AGENT (GENTAMICIN) IN MALE WISTAR RATS

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## OBJECTIVES

Many medications are under investigation as novel therapies to treat COVID-19. Among them, Hydroxychloroquine, Azithromycin, and Colchicine have been identified as potentially ototoxic. The aim of this study was to determine if these drugs, administered similarly to clinic protocols (route of administration, doses, and regimen schedule), have any effects on hearing. A reference compound, Gentamicin, well-known for its ototoxic effects, was used for comparative purposes.

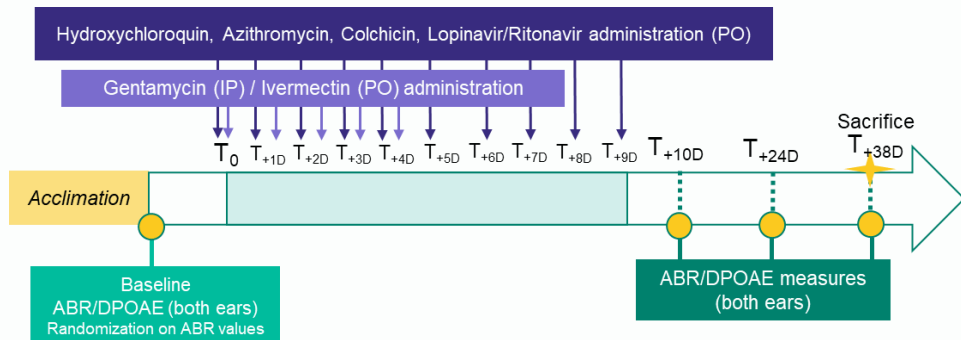
## METHODS

**Study Groups:** Male wistar rats (Janvier labs) were randomly divided into seven groups: one sham group (no treatment), five groups treated with either Hydroxychloroquine (62 mg/kg, per os once a day for five days), Azithromycin (51.5 mg/kg, per os once a day for five days), Colchicine (0.1 mg/kg, per os once a day for five days), Lopinavir / Ritonavir (41.5 mg/kg / 10.5 mg/kg, per os twice a day for ten days), Ivermectin (0.2 mg/kg, per os once a day for five days) or one group treated with Gentamicin (160 mg/kg, ip injection once a day for five days).

**ABR:** Auditory Brainstem Responses (both ears) were measured (eight animals/one ear) at baseline ( $T_0$ ),  $T_{+10\text{DAYS}}$ ,  $T_{+24\text{DAYS}}$  and  $T_{+38\text{DAYS}}$  at 5 frequencies: 4, 8, 16, 25 and 32 kHz. The signals were amplified (gain 10 000, band pass 100-5000 Hz). The stimuli consisted of tone pips (1 ms linear rise/fall time) presented in 10 dB steps from 90 to 0 dB.

**DPOAE:** The Distortion Product Otoacoustic Emissions were assessed (one animal/one ear at a time) at 4, 8, 16, 24 and 32 kHz at an intensity of 63 dB at the same time points.

### Study Scheme



### DPOAE

DPOAE amplitudes decreased in the Azithromycin treated group only at 32 kHz at  $T_{+38\text{DAYS}}$  compared to the Sham group, but no difference was observed in the Hydroxychloroquine, Colchicine, Lopinavir / Ritonavir and Ivermectin treated groups throughout the study. In the Gentamicin treated group, a significant decrease of DPOAE amplitudes measured at 45 dB and 63 dB was observed at 32 kHz at  $T_{+38\text{DAYS}}$  compared to the Sham group

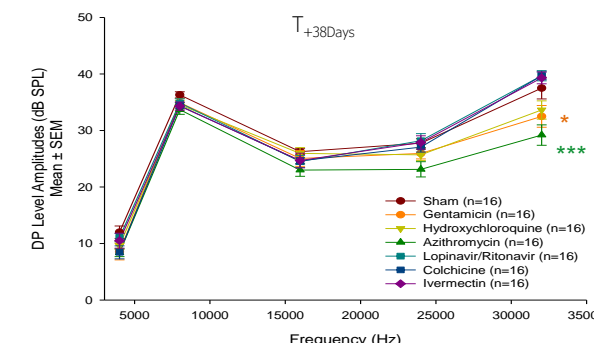
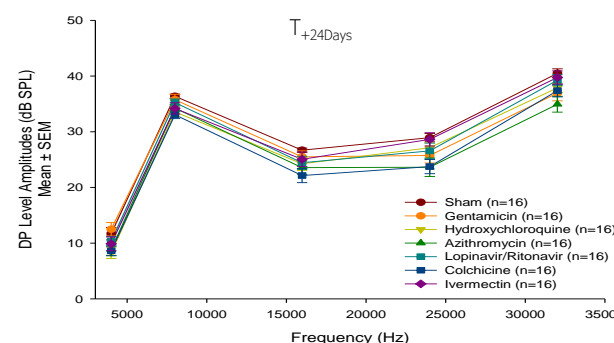
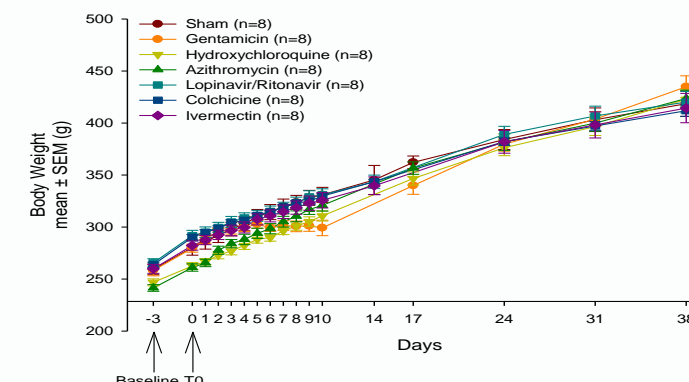
### ABR

In the Hydroxychloroquine, Azithromycin and Colchicine treated groups, a significant increase of ABR thresholds was observed for at least one frequency from  $T_{+24\text{DAYS}}$  compared to the Sham group. Conversely, in the Lopinavir / Ritonavir and Ivermectin treated groups, no significant increase of ABR thresholds was observed. In the Gentamicin treated group, a significant increase of ABR thresholds was observed at high frequencies compared to the Sham group from  $T_{+24\text{DAYS}}$ .

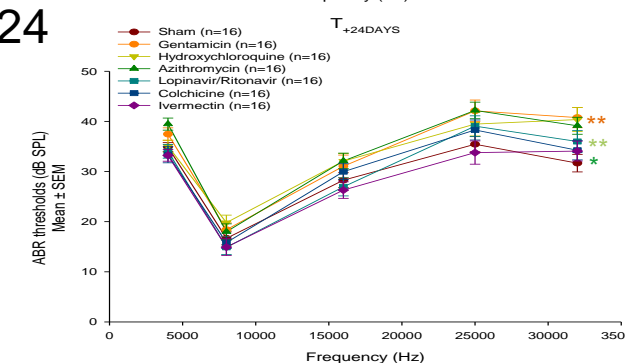
## RESULTS

### Body weight

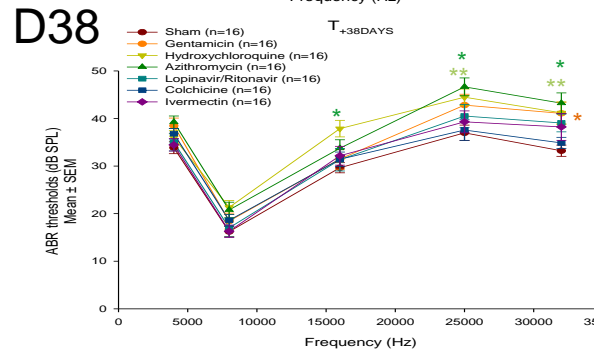
All animals exhibited similar body weight at baseline and throughout the study, except for the Gentamicin treated group, which exhibited a statistically significant decrease of body weight from  $T_{+8\text{DAYS}}$  to  $T_{+10\text{DAYS}}$ .



### D24



### D38



## CONCLUSION

Among the COVID-19 therapies, only Hydroxychloroquine and Azithromycin induced slight modifications of hearing late after the treatment period, progressively. Colchicine, Lopinavir / Ritonavir and Ivermectin had no effect in our experimental conditions. The effects of the ototoxic reference drug, gentamicin, were mild and limited to high frequencies. Additional work is necessary to pursue the characterization of the ototoxicity of these compounds in the long term, notably on hidden hearing loss.