Repurposing Amantadine and Memantine for COVID-19: Membrane-Associated Guanylate Kinases Might Evolve Novel SARS CoV-2 and Anticancer Therapeutics.

Short title:

Repurposing Amantadine and Memantine for COVID-19

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The author declares that there is no conflict of interest.

Guanylate kinase 1 (GK) was suggested to play a fundamental role in SARS CoV-2 replication (*1*) and other colleagues have confirmed its role in SARS CoV-2 replication while adding more targets to be considered(*2*). However, specific GK inhibitors e.g., the nucleotide analogue Ap5G, were only used experimentally and owing to the various physiological known and potentially yet to be discovered functions of GK, we suggest that its specific inhibitors should be carefully assessed as regards to their safety to manage COVID-19.

On the other hand, genetic variants of other kinases were described to negatively impact their action (*3*), and we postulate that GK genetic polymorphisms might help to further explain some idiosyncratic COVID-19 morbidity and mortality outcomes(*4*). Moreover, overexpression of GK gene was suggested to be involved in the pathogenesis of some tumors together with an unfulfilled call to discover some GK unexplored physiological functions (*5*) and we repeat this call.

In our opinion, non-authentic membrane-associated guanylate kinases (NAMAGKs), that contain GK like domains, might also share in SARS CoV-2 pathogenesis. NAMAGKs regulate the CNS NMDA receptors and their potential SARS CoV-2 interaction should be investigated especially if the preliminary reports showing a potential benefit of the NMDA receptor antagonist adamantanes; amantadine and memantine, proved clinically significant (*6*). Notably, amantadine, which is currently used in treatment of parkinsonism and was used in treatment and prophylaxis of influenza A virus infection, has been suggested to benefit COVID-19 patients (*7, 8*) and we postulate that SARS CoV-2 is still naïve and that amantadine SARS CoV-2 antagonism might involve inhibition of NAMAGKs and/or GK,

to be also noted that invitro antineoplastic properties of amantadine have been previously described.

Similarly, memantine, a dimethyl derivative of amantadine, an EMEA and FDA approved drug for treatment of moderate to severe Alzheimer's disease, has been suggested to possess beneficial COVID-19 effects via several mechanisms (*9*). Memantine possesses a higher affinity and more potent antagonism towards NMDA receptors than amantadine, thus the same or potentially better, interaction with NAMAGKs or GKs might be also applicable. Notably, both drugs have been suggested for COVID-19 management basing on their anti-inflammatory and immune-modulatory properties(*10*) as well as potential beneficial lysosomal dependent and neuroprotective effects(*11*).

Finally, as amantadine use is FDA approved in children one year of age and older with an acceptable side effects profile(*12*), we recommend amantadine to be be first considered for selected pediatric severe to critical COVID-19 patients who are in desperate need for COVID-19 effective drugs and we recommend testing memantine, before amantadine, for the adult and geriatric severe to critical cases and we opted for it over amantadine as we suggest it has better pharmacokinetic/dynamic and lower adverse effects profiles especially in the geriatric population(*13-15*), while carefully considering the potential contraindications, dosage modifications and drug-drug interactions in all cases.

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