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LETTER TO THE EDITOR

RAAS inhibitors in COVID-19: Not all are created equal. Telmisartan is the one

Inibidores de RAAS em COVID-19: nem todos são criados iguais!: Telmisartan é o único

Following the review article by Gonçalves et al.[1] on the potential use of renin–angiotensin–aldosterone system inhibitors to reduce the severity of COVID-19, Kow et al. published a comment on it in a Letter to the Editor, stating their general agreement but with some specific critical considerations.[2] Among these, they suggest that the partial peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist action of telmisartan could be the cause of the therapeutic benefit observed in patients with COVID-19. Gonçalves et al. subsequently replied.[3] The interesting debate that ensued stimulated our interest in highlighting some pharmacological properties of telmisartan. To our knowledge, these properties enable it to be considered the best agent among the available angiotensin receptor blockers (ARBs) to reach peripheral tissues in effective concentrations to antagonize the inflammatory process triggered by the SARS-CoV-2 virus, after its administration in high therapeutic doses.[4,5]

Telmisartan is the most lipophilic ARB (its partition coefficient is approximately 100 times higher than that of losartan and more than 10 000 times higher than that of EXP3174, the active metabolite of losartan).[4] Telmisartan is the ARB with the highest volume of distribution (500 l), which enables its extensive binding to peripheral tissues,[4] and with the longest plasma half-life (24 h, as opposed to 2 h for losartan), undergoing accumulation in peripheral tissues until it reaches a steady state at 4–5 days.[4] Seven days after daily administration of 160 mg orally in hypertensive patients, telmisartan reaches a maximum plasma concentration of 2871 ng/ml.[6] Bearing in mind that the molecular weight of telmisartan is 514.61, these values correspond to 5.58 μM.

Telmisartan is a more potent ARB than losartan: affinity estimates (pKi or pIC50) at mammalian AT1 receptors are 8.33 and 7.71, respectively.[7] In addition, telmisartan dissociates from the AT1 receptor in an apparently irreversible manner (AT1 receptor dissociation half-life: 213 min; AT1 receptor dissociation half-life of losartan: 67 min and EXP3174: 81 min).[7] Based on its long plasma half-life and its slow dissociation of the AT1 receptor, telmisartan behaves in clinical practice as an irreversible antagonist.

Telmisartan is a partial agonist at PPAR-γ receptors with a 10-fold greater potency than losartan (telmisartan EC50: 5 μM; losartan EC50: 50 μM). After administration of telmisartan at a daily dose of 160 mg, it reaches a maximum plasma concentration of 5.58 μM at seven days. Based on its high lipophilicity and high volume of distribution, it is reasonable to assume that telmisartan concentrations in peripheral tissues will be higher than those in plasma.

In summary, it is considered that telmisartan at therapeutic doses, in addition to blocking AT1 receptors, stimulates PPAR-γ causing additional anti-inflammatory effects.[8–10]

Conflicts of interest

The authors have no conflicts of interest to declare.

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