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Review article

A monograph on Perampanel

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ABSTRACT

Perampanel is a non-competitive antagonist at the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subtype of ionotropic glutamate receptor. It is approved as an adjunctive therapy in focal epilepsy with or without secondarily generalised seizures in patients aged >12 years. This in-depth review describes the structure, mechanism of action, pharmacokinetic profile, indications, dosage and efficacy, contraindications, possible drug interactions, adverse effect profile and its management with regards to Perampanel. It is one of the latest additions in the therapeutic armamentarium of an epileptologist being useful in focal as well as generalised epilepsies as an add-on. It has shown high rates of efficacy and a relatively good tolerability. Slow dose titration, patient education and bed time dosing along with downtitration of medications which may aggravate Perampanel associated adverse events improves the patients' compliance and quality of life.

1. Introduction

15 new compounds have been introduced into the antiepileptic armoury over the past two decades.[1] Notwithstanding this development, focal seizures remain uncontrolled in more than 30% of the cases.[2] Focal seizures are notorious for their tendency to remain uncontrollable despite treatment, thus making a combination therapy in such cases essential. On the flip side however, is the ever-increasing concern regarding adverse effects and neurotoxicity of polypharmacy – especially when using a combination of drugs with a similar mode of attack.[3] Hence, newer drugs with novel modes of action are the need of the hour to improve seizures control without augmenting the pre-existing probability of adverse events. Clinical trials which are essential for introduction of any drug into the routine clinical practice, may not reflect the day to day usage by a clinician, making it essential for everyone to understand the efficacy and safety profile of individual drugs.[4–7]

Conventionally, N-methyl-D-Aspartate (NMDA) was the prime target of interest for reducing neuronal excitability due to its key role in synaptic potentiation. But it was later discovered that normally functioning NMDA receptors were essential for vital higher processes like formation of memory. Memory deficits and learning disabilities may be side effects of NMDA antagonism.[8,9] Hence, newer drugs which target non-NMDA receptors may have better acceptability.

Perampanel or chemically 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3) with a molecular formula C23·H15·N3O·¾H_2O (molecular mass 362.90) (Fig. 1) acts through selective non-competitive antagonism of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) which is a major subtype of the ionotropic glutamate receptors. Three pivotal clinical trials found Perampanel to be effective in refractory partial onset seizures.[10,12] It has also been approved as an adjunct for primary generalised tonic clonic seizures (GTCS). Dizziness, somnolence, and fatigue are the major dose related side effects. FDA approval was given for its usage in partial and primary generalised tonic clonic seizures for patients who are older than 12 years of age.

2. Mechanism of action

AMPA receptors post-synaptically mediate excitatory neurotransmission of glutamate and thus play a crucial role in epileptogenesis. Glutamate, once released pre-synaptically binds to the AMPA receptors in the post-synaptic neurons and opens several cation channels causing post-synaptic depolarisations called excitatory post-synaptic potentials (EPSPs) (Fig. 2).

Spatial or temporal summation of these potentials on reaching the threshold, trigger an action potential in these neurons thus

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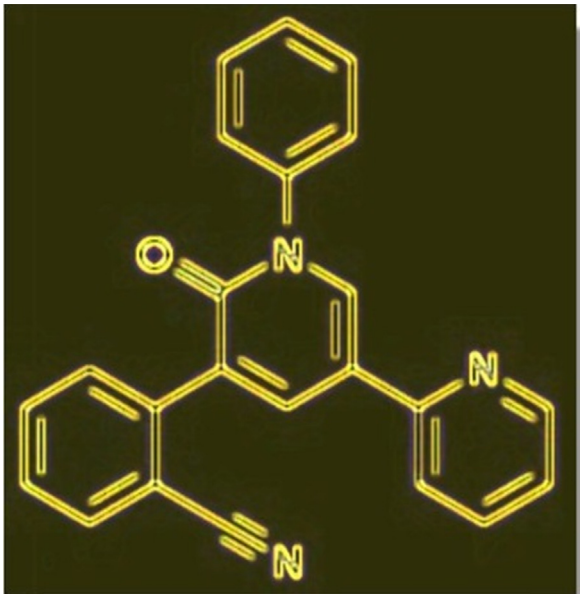

Fig. 1. Structure of Perampanel.

completing the information transfer to the post-synaptic neurons. Thus, Perampanel by acting as a non-competitive negative allosteric antagonist (Fig. 3) at these AMPA receptors reduce post-synaptic neuronal excitability and thereby increases the seizure threshold.[13] Being a selective antagonist, other glutamate receptors–NMDA (N-methyl-D-aspartate) and kainate are unaffected.[14]

3. Pharmacokinetics

Route of administration is oral with a rapid and complete absorption. Rate of absorption may decline with food. C_{max} decreased by 28–40% and T_{max} delayed by 2–3 h with food (Fig. 4). First pass metabolism is negligible. The area under the curve (AUC, implying the extent of drug absorption) shows a dose proportional increase after single and multiple doses.

The terminal half-life of Perampanel is 105 h and hence the steady state is attained in 2–3 weeks. It is 95% bound to albumin and alpha 1-acid glycoprotein. Blood to plasma ratio of perampanel is 0.55–0.59. Compared to Talampanel, another AMPA receptor antagonist, the longer half-life of Perampanel allows once a day dosage. A clearance rate of 12 ml/min (0.72 l/h) was observed in healthy subjects. Though no gender based dosage adjustment is required, the clearance rate of Perampanel was 18% lower in females when compared to males. It is metabolised primarily through CYP3A4 and CYP3A5 and to a lesser by CYP1A2 and CYP2B6. Hence plasma levels decline to 50–67% with concomitant use of known CYP inducers. 48% is excreted in faeces and 22% in urine as a mixture of oxidative and conjugated metabolites.

In patients with hepatic impairment, plasma drug levels were 50% higher in patients with mild hepatic impairment (Child – Pugh A). An increase of 225% occurs in patients with a moderate

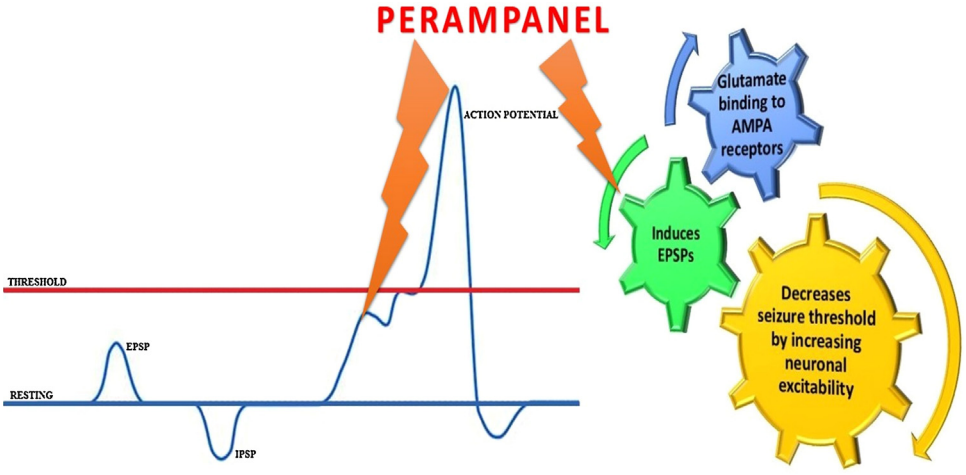

Fig. 2. Mechanism of action.

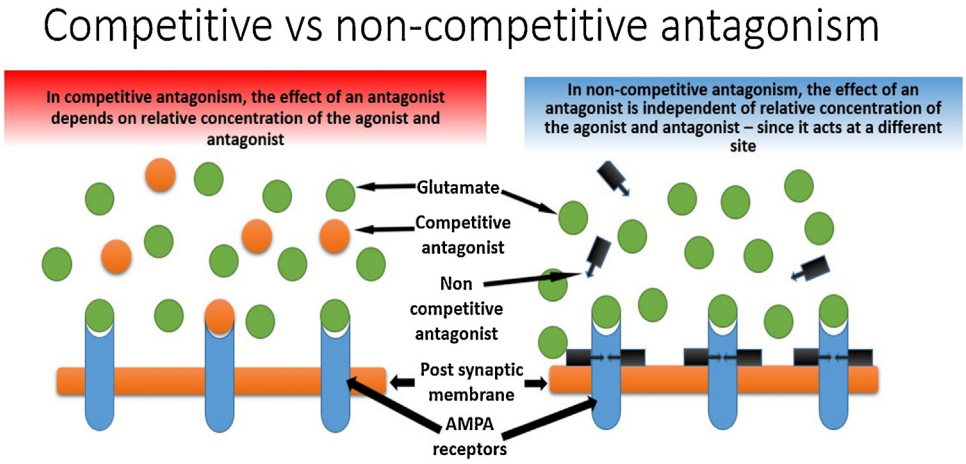

Fig. 3. Competitive vs non-competitive antagonism.