CLINICAL PHARMACOLOGY

Tolperisone

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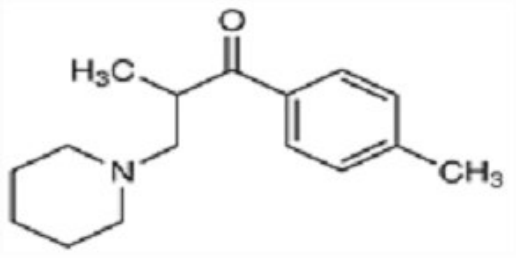
The upper motor neuron dysfunction occurs in cases of cerebral palsy, spinal cord injury, stroke, multiple sclerosis with spasticity as the commonest manifestation and it interferes with the patients functional capacity and day to day activities.[1] Spasticity is due to the interruption of cortical inhibitory descending spinal motor pathways. The quality of life in these patients can be improved by symptomatic therapy which can be achieved by muscle relaxants. Commonly used drugs are baclofen, diazepam, tizanidine, dantrolene and gabapentin which act centrally. These drugs relieve spasticity but produce sedation, muscle weakness, impairment of co-ordination, depression, mental confusion and withdrawal phenomenon.[2] Hence there is the need for an antispastic agent devoid of the above mentioned side effects. Studies have shown that Tolperisone can overcome these side effects. Tolperisone is available in Europe, Africa and Asia. It is not marketed as yet in the United States of America.

Chemistry

Chemically, Tolperisone is 1-piperidino-2-methyl-3-p-tolyl-propanone-3 similar to lidocaine. The compound was first developed in Hungary. It is structurally similar to lidocaine. The other analogs are eperisone, lanperisone, inaperisone, silperisone. The enantiomers of tolperisone are dextrorotatory (+) with predominant muscle relaxant activity and levorotatory (-)-isomer which relaxes bronchial and vascular smooth muscle but clinically used tolperisone is a racemic mixture.



Mechanism of action

The pathophysiology of spasticity is not clearly understood but it could possibly be due to loss of inhibitory control of the corticospinal tract which controls the alpha motor neurons through monosynaptic and polysynaptic pathways, which would result in over activity of the alpha motor neuron.[2]

Studies have shown that tolperisone can block the voltage dependent sodium channels in the neuron and thus prolongs the inactivated state of the sodium channels and also the refractoriness.[3] Tolperisone also blocks the calcium channels in a frequency dependent manner in the presynaptic nerve terminal. This presynaptic inhibition occurs in dorsal root ganglia cells at a higher concentration. Tolperisone-type muscle relaxants exert their spinal reflex inhibitory action predominantly via a presynaptic inhibition of the transmitter release (glutamate) from the primary afferent endings via a combined action on voltage-gated sodium and calcium channels.[4] A decreased transmitter release results in depression of EPSP (excitatory post synaptic potential). Other mechanisms include antagonism of intracellular calcium release from sarcoplasmic reticulum and interference with prostaglandin biosynthesis (anti-inflammatory action).[1] Tolperisone thus inhibits monosynaptic and polysynaptic reflexes due to its depressant and membrane stabilising mechanism.

Pharmacokinetics

The recommended oral dose for adults is 150 to 450 mg per day in two or three divided doses. It can be administered intramuscularly 100 mg every 12 hours and intravenous once a day. After oral administration absorption and distribution of tolperisone is rapid with large variation in AUC (area under curve) and Cmax (peak concentration).[5] Tolperisone is mainly metabolised by p450-mediated CYP2D6 metabolic pathway into its active metabolite hydroxymethyl tolperisone.[6] The half life of the drug is 1.5 hrs, it undergoes extensive metabolism and only 0.1% of total dose appears in urine over a period of 24 hrs.[5] The inter-individual variation in the plasma concentration is due to the genetic polymorphism of the drug metabolising enzymes.[6] Hence the dose of tolperisone needs to be individualised.

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Adverse effects

Commonly encountered side effects due to tolperisone are abdominal pain, nausea, diarrhoea, dizziness, headache, weakness, tremor, muscle pain. It has been reported that it can manifest with hypersensitivity reactions ranging from urticaria to arterial hypotension. These reactions have been reported to occur within one hour after oral administration. The hypersensitivity reactions could be due to the intrinsic vasodilator activity of the drug.[7]

Caution need to be exercised in patients with hypersensitivity to tolperisone, hepatic failure, myasthenia gravis and in pregnancy.

Uses

1. Spasticity due to damage to the pyramidal tract, myelopathy, encephalomyelitis, multiple sclerosis, neurolathyrism.[8]
2. Muscular dystonia due to spastic paralysis (stroke)[9] and encephalopathies.
3. Muscular hypertonicity and muscular contractions due to spondylosis, spondyloarthrosis, cervical and lumbar syndromes, arthrosis of large joints.
4. Central spinal pain, neuropathic pain (sodium channel blockade), tension headache, low back pain, cervical pain, fibromyalgia.[1]
5. Peripheral vascular diseases like obliterating atherosclerosis of extremity vessels, diabetic angiopathy, thromboangitis obliterans, raynaud's syndrome.[1]

Clinical trials:

Melka et al 1997 have shown a symptomatic improvement in 72 patients suffering from neurolathyrism and the adverse effects that occurred were self limiting.[8] A placebo-controlled double blind clinical trial to evaluate the sedative effect of single and repeated doses of 50mg and 150mg tolperisone for 8 days on 72 healthy male young adults showed no sedative action and also did not impair reaction times.[10] Stamenova et al 2005 studied the effects of tolperisone on spasticity following cerebral stroke and have demonstrated the efficacy and excellent tolerability at $\geq$ 450 mg based on individual titration of the dose.[9] Bae, Kim, Park et al have shown considerable inter-individual variation in the pharmacokinetics of tolperisone in young healthy adults so that dose has to be individualised.[5]

CONCLUSION

Spasticity requires treatment only if it interferes with the functional activity, causes discomfort and impairs hygiene. Treatment options include non-pharmacological measures such as physiotherapy and procedural interventions such as surgery and nerve block. Tolperisone is a novel antispastic drug with advantages over the existing drugs because it does not act through adrenergic, cholinergic, GABAergic and serotoninergic receptors, hence there is no sedation, drowsiness, weakness, changes in mood and cognition. To conclude tolperisone represents an effective and safe treatment option for the management of post cerebral stroke spasticity, neurolathyrism and painful reflex muscle spasm.

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