Introduction:

Gabapentin was introduced in 1994 as an adjuvant antiepileptic drug. Of late, it has found applications as a broad spectrum analgesic and as a multimodal perioperative drug.

Pharmacology:

Chemistry: It is [1-(amino methyl)cyclohexane acetic acid] and a structural analogue of Gamma amino butyric acid. It is a white crystalline solid, freely soluble in water.

Structure:

Pharmacokinetics:

The absorption of Gabapentin is dose dependent due to a saturable transport system. It is extensively distributed in human tissues & fluids after oral administration. After a single oral dose of 300mg, peak plasma concentrations are attained in 2-3hrs. The bioavailability of a single 300mg oral dose is 60% & decreases with increase in dose. The plasma concentrations are proportional with dose upto 1800mg daily & then plateau at approximately 3600mg daily. It does not bind to plasma proteins & is not metabolized. It is eliminated unchanged in urine. The elimination half-life after a single oral dose of 200-400mg is 5-7hrs. It crosses the blood brain barrier rapidly.

Pharmacodynamics:

Action on nervous system:

Gabapentin produces analgesia, anxiolysis & sedation. It is proposed that it increases the concentration & rate of synthesis of GABA in brain.

The exact mechanism of action is not well understood but its analgesic efficacy & safety has been demonstrated in physiological & pathological pain. Despite its structural similarity with GABA it does not act via mechanism related to GABA. Possible pharmacologic targets of Gabapentin are selective activation of the GABAB receptors, enhancement of N-methyl-D-aspartate(NMDA) currents, blocking AMPA receptor mediated transmission in the spinal cord. At clinically relevant concentration it reduces the membrane voltage gated Ca currents (VGCC channels) in dorsal horn ganglion neurons. It has a high affinity for the αδ subunit of the pre-synaptic VGCC channels which inhibit calcium influx & subsequent release of excitatory neurotransmitters by sensory neurons. It increases serotonin concentration in brain. Gabapentin does not affect nociceptive thresholds but has a selective effect on nociceptive process involving central sensitization. Central sensitization plays an important role in amplification of post operative pain.

Action on CVS:

Only few data in literature are available regarding the effect of gabapentin on CVS. 1200 mg administered orally 1 hr before surgery has no effect on the mean BP & HR of patient 0-24 hrs after operation.

Formulation & routes of administration:

Gabapentin is currently not available parenterally. It is available in tablet & capsule form in the strength of 300 & 400mg usually in combination with methcobolamin. (Movapentin, 'Neurontin')

Side effects:

It is a well tolerated drug with a favourable side effect profile. Side effects include dizziness (10.9%), somnolence (15.2%), nausea (3.2%), ataxia (2.6%), tremor, asthenia (6%), weight gain (2.6%), ambiopyia (2.1%). These effects usually are mild to moderate in severity but resolve within 2 weeks of onset during continued treatment. Withdrawal symptoms may occur after abrupt discontinuation of high dose Gabapentin.

Clinical uses of Gabapentin:

1. Non anaesthetic and 2. Anaesthetic

Non anaesthetic uses of Gabapentin:

1. As an anti-epileptic: Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures at dosages that range upto 2400mg/day.
2. In psychiatric patients with comorbid anxiety related disorders, Gabapentin has long term anti-anxiety & hypnotic effects.
3. To decrease hot flushes in post-menopausal women. Anaesthetic uses of gabapentin:

1. In the treatment of neuropathic pain:

Gabapentin can be used for the symptomatic treatment
of painful diabetic neuropathy, as an adjunct to opioid analgesia for neuropathic cancer pain, for the treatment of post herpetic neuralgia, trigeminal neuralgia, chronic regional pain syndrome, HIV related neuropathy, headache\textsuperscript{12,13} post poliomyelitis neuropathy\textsuperscript{14} & other chronic pain states. 30-1200mg three times daily is the recommended dose for neuropathic pain.

2. Peri-operative analgesia:
   I) For post operative analgesia: As an analgesic both at rest & with movement. It decreases analgesic consumption & opioid related adverse effects but with increased incidence of sedation & dizziness.\textsuperscript{15} Doses ranging from 300-1200mg given orally 1-2hrs before surgery have been found to be effective in reducing post operative opioid consumption in the first 24hrs after surgery & to a lesser extent in reducing pain scores.\textsuperscript{16} 1200mg oral gabapentin given 1 hr before ambulatory ENT surgery done under LA & MAC provides significant analgesia.\textsuperscript{17} Premedication with Gabapentin reduces tourniquet pain and the quality of IVRA.\textsuperscript{18} Perioperative oral Gabapentin is a useful adjunct for the management of postoperative pain that provides analgesia through a different mechanism than opioids & other analgesics thus making it a reasonable addition to a multimodal analgesic treatment plan.\textsuperscript{19}
   ii) As a pre-emptive analgesic: Gabapentin elevates pain threshold & prevents acute nociceptive & inflammatory pain especially when given before trauma.\textsuperscript{20} Several workers have found that 300-1200mg oral gabapentin given 1 hr before surgical stimulus significantly reduces the incidence of pain & post op opioid consumption without significant side effects.\textsuperscript{21} Pre-operative oral Gabapentin 300mg has been found to reduce the number of post operative epidural bolus doses in the initial 24 hours in patients undergoing abdominal hysterectomy.\textsuperscript{22} In infraumbilical surgery, in absence of opioid or non opioid analgesics, pre operative Gabapentin prolongs the analgesic effects of spinal analgesia & reduces the doses of peri operative analgesics.\textsuperscript{23}

3. To attenuate haemodynamic response to direct laryngoscopy and endotracheal intubation\textsuperscript{24,25} 800mg gabapentin 1-2 hrs before surgery effectively attenuates the increase in MAP & IOP in the first 10 min of laryngoscopy & endotracheal intubation. The mechanism is unknown. It inhibits membrane VGCCs, thus acting like a calcium channel blocker.\textsuperscript{26} Some studies have shown that Gabapentin has no effect on heart rate whereas some have shown that it decreases heart rate. No data are available on the possible role of Gabapentin in the attenuation of other aspects of the stress response to surgery.

4. For pre operative anxiolysis: Gabapentin pretreatment has been reported to produce significantly lower pre operative VAS anxiety scores and to thus allay pre op anxiety.\textsuperscript{27}

5. Prevention of nausea & vomiting: 600mg oral gabapentin 2 hrs before surgery effectively suppresses nausea & vomiting eg: in laparoscopic cholecystectomy. Gabapentin is also effective in reducing acute & delayed onset nausea & vomiting in patients on chemotherapy\textsuperscript{28} by mitigating tachykinin neurotransmitter activity.

6. Prevention of post operative delirium: The incidence of post operative delirium has been found to be less in patients on peri operative Gabapentin. The mechanism is unknown and may be related to the opioid sparing effect of Gabapentin.\textsuperscript{29}

7. Prevention of chronic post surgical pain (CPSP): The effective treatment of acute pain is usually not associated with the prevention of chronic pain.\textsuperscript{30} CPSP is particularly common after limb amputation, inguinal hernia repair, breast surgery & thoracotomy.\textsuperscript{31} Peri operative Gabapentin (starting day before surgery & continued for 3-30 days post op) with or without combining with local wound infiltration of local anaesthetic like Ropivacaine / EMLA cream prevents the development of CPSP after limb amputation, breast & abdominal surgeries.\textsuperscript{32}

8. Intrathecal use: Intrathecal Gabapentin reduces tactile allodynia & hyperalgesia in animal models of incisional & thermal injury.\textsuperscript{33}

Conclusion:
Gabapentin is a drug with multi modal effects having various peri operative applications and occupying an important place in the pain and palliative care clinic. It has well established its place in the treatment of neuropathic pain, as an adjunct for post operative pain relief, as a pre-emptive analgesic & in the prevention of chronic post surgical pain. Studies regarding the effects of Gabapentin on hemodynamic response to tracheal intubation, prevention of PONV, reducing post operative delirium, pre op anxiolysis, intra thecal use and as an adjunct to regional nerve blocks are going on and the results are promising but, as yet, inconclusive. Of late, Gabapentin is being increasingly compared with the newer synthetic GABA analogue ‘Pregabalin’ in terms of outcome, benefits, side effects and as a part of the multimodal approach to pain management.

References:


10. Anil Verma et al To evaluate the role of Gabapentin as pre-emptive analgesic in patients undergoing total abdominal hysterectomy in epidural anaesthesia. IJA 2008;52(4):428-431.


