GABAPENTIN

Class: Anti-epileptic.

Indications: Adjunctive treatment for partial seizures with or without secondary generalization;^{1,2} post-herpetic neuralgia, †other types of neuropathic pain,³⁻¹² †hot flashes.

Pharmacology

Gabapentin is a chemical analog of γ -aminobutyric acid (GABA) but does not act as a GABA-receptor agonist. It binds to a specific site in the CNS, gabapentin-binding protein, and interacts with the $\alpha 2\delta$ subunit of calcium channels in the CNS.¹³ It increases GABA synthesis and release but its exact mechanism of action as an antiepileptic is complex and not fully understood. Absorption is by a saturable mechanism and bio-availability is more than halved as the dose increases from 100mg to 1200mg. Antacids containing **aluminum** or **magnesium** reduce gabapentin bio-availability by 10–25%. It is not protein-bound and freely crosses the blood-brain barrier. It is excreted unchanged by the kidneys and cumulates in renal impairment. The halflife increases to 50h when creatinine clearance is <30ml/min, and to over 5 days in anuria. Initial drowsiness or dizziness occurs in 50% of patients and generally resolves over 7–10 days of use.¹² Gabapentin has few drug interactions. **Cimetidine** impairs the renal excretion of gabapentin but not to a clinically important extent. It does not interact with anti-retroviral antibiotics.

Gabapentin is widely used for neuropathic pain.^{3-10,12} However, there is no evidence that it is more effective than older anti-epileptics.¹⁴⁻¹⁶ Further, in an open study in diabetic neuropathy, although gabapentin provided better relief than **amitriptyline**,¹⁷ an RCT did not detect a difference.¹⁸

Benefit has been reported in patients with cancer-related neuropathic pain when given together with opioids,¹⁹ reflecting the positive benefit shown in animal studies.²⁰ However, although the percentage of patients whose pain reduced by $\geq 1/3$ was significantly higher during the first 5 days in those receiving gabapentin, after 10 days there was no difference (62% vs. 64%). Further, although significantly different after 10 days, the daily average global and dysesthesia pain scores differed by ≤ 1 point out of 10 (e.g. average global pain, gabapentin 4.6, placebo 5.5), and there was no significant difference in the scores for lancinating (stabbing) and burning pain. Thus, in cancer-related neuropathic pain, the magnitude and duration of the benefit of gabapentin appears disappointing.²¹

In amyotrophic lateral sclerosis (motor neuron disease), gabapentin 800mg t.d.s slowed decrease in arm strength marginally (p>0.5) over a 6-month period.²² It reduces spasticity and muscle spasm in multiple sclerosis.^{23,24} There is a report of gabapentin abolishing opioid-related myoclonus.²⁵

Bio-availability PO 100mg, 74%; 300mg, 60%; 600mg, 49%; 1200mg, 33%.

Onset of action 1–3h.

Time to peak plasma concentration 2-3h PO.

Plasma halflife 5–7h; 2 days or more in moderate–severe renal impairment, 5 days in anuria, 3–4h during hemodialysis.

Duration of action probably 8–12h, much longer in severe renal impairment/failure.

Cautions

Renal impairment; absence seizures (may worsen); psychotic illness (may precipitate psychotic episodes, generally resolving on dose reduction or discontinuation); **aluminum**- and **magnesium**-containing compounds reduce bio-availability; false positive readings for urinary protein with Ames N-Multistix SG®. **Morphine** and **naproxen** may increase gabapentin levels; high doses of gabapentin may decrease **hydrocodone** levels (mechanisms unknown).

Undesirable effects

For full list, see manufacturer's PI.

Very common (>10%): drowsiness, dizziness.

Common (<10%, >1%): amnesia, anxiety, fatigue, amblyopia, diplopia, nystagmus, dysarthria, ataxia, tremor, arthralgia, myalgia, peripheral edema, weight gain, dry mouth, pharyngitis, dyspepsia, diarrhea.

Uncommon (<1%, >0.1%): leucopenia, impotence, gynecomastia.²⁶

Dose and use

Gabapentin should *not* be given at the same time as antacids containing **aluminum** or **magnesium**; *give at least 2h apart*.

Neuropathic pain

For neuropathic pain, a rapid upward titration is suggested in the PI (Table 4.1). However, in order to reduce undesirable effects, a slower titration of the initial dose of gabapentin over several weeks is advisable in debilitated and elderly patients, those with renal impairment (see below) or if receiving other CNS depressant drugs.^{12,27}The dose is titrated to achieve greatest benefit without unacceptable undesirable effects. The maximum approved dose for neuropathic pain and epilepsy is 1800mg/day, but up to 3600mg/day has been used for both indications. The dose of gabapentin should be reduced in adults with renal impairment and those on hemodialysis (Table 4.2).²⁷ As creatinine clearance declines with age, the maximum tolerated dose is likely to be lower in the elderly, e.g. 1200mg/day. If required the capsules can be opened and the contents mixed with water, fruit juice, apple sauce, etc.²⁸

	Rapid ^a		Slow			
Day 1	300mg h.s.	Day 1	100mg t.i.d.			
Day 2	300mg b.i.d	Day 7	300mg t.i.d.			
Day 3	300mg t.i.d.	Day 14	600mg t.i.d.			
Then increase by 300mg/day every 3 days as needed up to 400–1200mg t.i.d.						

Table 4.1 Neuropathic pain: dose escalation of gabapentin (normal renal function)

a. for recommendations for epilepsy, see manufacturer's PI.

Creatinine clearance (ml/min)			Starting dose ^a	Maximum dose	
>60			300mg t.i.d.	1200mg t.i.d.	
30–59			200mg b.i.d.	700mg b.i.d.	
15–29			200mg q.d.	700mg q.d.	
<15 ^b			100mg q.d.	300mg q.d.	
Supplementary	sinale	dose	after 125–350mg ^c		

Table 4.2 Impact of renal impairment on starting and maximum doses (see also PI)

every 4h of hemodialysis

a. smaller starting dose is advisable in elderly patients and those receiving other CNS depressant drugs (see text)

 b. for creatinine clearance <15ml/min, further reduce daily dose in proportion to creatinine clearance; thus if creatinine clearance 7.5ml/min, give half the dose recommended for creatinine clearance 15ml/min

c. in practice, round dose up or down to convenient tablet size or solution volume.

Hot flashes

- start with a low dose, as for neuropathic pain
- if necessary, increase to 300mg t.i.d.²⁹

Stopping gabapentin

To avoid precipitating seizures or pain, gabapentin should be withdrawn gradually over ≥ 1 week.

Supply

Gabapentin (generic)

Capsules 100mg, 300mg, 400mg, 28 days @ 300mg t.i.d. = \$56.

Tablets 600mg, 800mg, 28 days @ 300mg or 600mg t.i.d. = \$42 and \$84, respectively.

Oral solution 250mg/5ml, tentative FDA approval granted; price unavailable at time of going to press.

Neurontin® (Pfizer)

Capsules 100mg, 300mg, 400mg, 28 days @ 300mg t.i.d. = \$109. *Tablets* 600mg, 800mg, 28 days @ 600mg t.i.d. = \$205. *Oral solution* 250mg/5ml, 28 days @ 300mg t.i.d. or 600mg t.i.d. = \$127 and \$254, respectively.

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