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WHITE PAPER

Plasma concentration of oral gabapentin dose not increase proportionally with increase dosing

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Shanen Khwaja (Pharm.D)

Enovachem Pharmaceuticals

The gabapentinoids are often recommended as first-line treatments for the management of neuropathic pain.[1] The differing pharmacodynamic and pharmacokinetic profiles can have implications for clinical practice.[1] Gabapentin, as an oral preparation, is absorbed in the small intestine by a combination of diffusion and facilitated transport.[2] Oral bioavailability for gabapentin is between 30-60%.[1] As the dose of gabapentin increases, the area under the plasma concentration–time curve (AUC) does not increase proportionally.[1]

Gabapentin is absorbed in the small intestine. Absorption of gabapentin is solely dependent on L-amino acid transporters (LAT) that are easily saturable, resulting in dose-dependent pharmacokinetics.[1] Orally administered gabapentin exhibits saturable absorption--a nonlinear (zero-order) process--making its pharmacokinetics less predictable.[3] As this carrier-dependent transport is saturable, the bioavailability of gabapentin varies inversely with dose.[2] Plasma concentrations of gabapentin do not increase proportionally with increasing dose.[3]

The recommended starting dose in the treatment of neuropathic pain is 300 mg three times a day with titration if necessary to a maximum of 3600 mg/day but doses up to 4200 mg, have been reported.[2] The bioavailability of a 300mg dose is 60%, whereas that of a 600mg dose is 40% and this decreases to 35% at steady state with doses of 1600mg three times daily.[2] As a result of the dose dependent saturable absorption of gabapentin, Cmax increases less than threefold when the dose is tripled from 300 to 900mg.[2]

It is noteworthy to note, "the incidence of peripheral edema was increased when gabapentin was titrated to ≥1800 mg/d. Dizziness and somnolence, the other most commonly occurring adverse events, were transient and did not occur more frequently or worsen with titration to ≥1800 mg/d."[4]

In conclusion, since oral gabapentin has saturable absorption the pharmacokinetics is not that predictable because it follows zero-order kinetics, thus plasma concentration of gabapentin does not increase proportionally with increase dosing.[3] Gabapentin has a nonlinear relationship between therapeutic and toxic levels and exhibits a wide interpatient variability, making the analysis of plasma levels of limited use other than to confirm the presence of gabapentin.[5]

References:

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