

Why is there a limit on the dose and duration of use for carbamazepine suppositories?

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Background

Carbamazepine suppositories are licensed for short-term use as replacement therapy in patients whom oral treatment for epilepsy is temporarily not possible. The maximum recommended period is for 7 days. (1, 2)

Carbamazepine 125mg and 250mg suppositories are available and the maximum daily dose recommended by the manufacturer is limited to 1000mg (250mg every 6 hours). (1, 2) When switching from oral to rectal carbamazepine, the dosage of the latter should be increased by approximately 25%. For example, 100mg tablet corresponds to 125mg suppository, although the final dose adjustment should always depend on the clinical response in the individual patient. (1, 2)

Answer

The maximum daily dose for carbamazepine suppositories recommended by the manufacturer is based on its pharmacokinetic data. As measured by area under the curve calculations, the total bioavailability of carbamazepine suppositories is approximately 25% less than from oral carbamazepine formulations. For doses up to 300mg, approximately 75% of the total amount absorbed reaches the general circulation within 6 hours of insertion. It is for these reasons that the maximum recommended daily dose is limited to 250mg four times daily (1000mg per day), the equivalent to 800mg per day orally. (1, 2) A small pharmacokinetic study involving 22 children found that plasma concentration profiles for carbamazepine did not show any significant differences between oral and rectal administration when the suppository dose was increased by 25% compared to the tablet dose. (3)

The maximum recommended treatment period for carbamazepine suppositories is 7 days as clinical trials have only been carried out for this length of time. If the suppositories are used for longer than 7 days, there could be an increased risk of rectal irritation. (4-7) No published reports of using carbamazepine suppositories in adults for more than 7 days have been located.

A case report published in 2002 described the continuous use of rectal carbamazepine for 10 weeks in an 18 month old child. (8) The child, diagnosed with PEHO ("Progressive encephalopathy, oedema, hypersarrhythmia and optic atrophy") syndrome, was commenced on oral carbamazepine liquid at a dose of 100mg four times daily. After 5 months of oral carbamazepine, the child developed frequent and persistent vomiting due to marked gastro-oesophageal reflux (carbamazepine toxicity was excluded) which was resistant to anti-reflux and anti-emetic medication.

At this point, the child was commenced on intravenous phenobarbitone (dose not stated) and rectal carbamazepine suppositories at a dose of 125mg four times daily. Rectal carbamazepine was given for 10 weeks and remained at this dose.

Blood levels of carbamazepine remained stable following the introduction of the rectal formulation and there was no change in the patient's seizure control. Similarly, there was no obvious local (perianal) or systemic adverse effects after the first 8 weeks of rectal carbamazepine. However, by the end of the ninth week, the patient developed erythema and excoriation of their anus which was considered by the authors to represent a direct effect of the carbamazepine suppositories.

At this stage, the child's reflux had resolved and the rectal carbamazepine was gradually replaced with oral carbamazepine liquid over a ten day period. The intravenous phenobarbitone was also

converted back to an oral preparation. The change to oral carbamazepine and oral phenobarbitone was not associated with the development of any adverse effects and no change in the frequency of seizures was noted.

Summary

- The maximum recommended daily dose for carbamazepine suppositories is 1000mg (250mg four times daily) which is equivalent to 800mg per day orally. This maximum dosage is based on carbamazepine's pharmacokinetic data.
- The maximum recommended treatment period for carbamazepine suppositories is 7 days as clinical trials have only been carried out for this length of time.
- One case involving the rectal administration of carbamazepine suppositories for 10 weeks to an 18 month old child reported the development of erythema and excoriation of the anus after 9 weeks. This was felt to represent a direct effect of the carbamazepine suppositories.

Limitations

No published reports of using carbamazepine suppositories in adults for more than 7 days have been located.

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