Once-daily gastroretentive gabapentin for the management of postherpetic neuralgia: an update for clinicians

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Abstract: Gabapentin was originally developed as an add-on anticonvulsant drug, but has been widely used in the USA for the management of postherpetic neuralgia since its approval for this indication in 2002. Gabapentin has a short elimination half life and limited absorption due to a saturable L-amino acid transport system, which is expressed predominantly in the proximal small intestine. Hence, the original immediate-release gabapentin formulation (gabapentin TID) must usually be taken three times a day for optimal efficacy. Gabapentin TID is also associated with a high incidence of dizziness and somnolence and some patients are unable to tolerate the doses required for maximum pain relief. A once-daily, gastroretentive formulation of gabapentin was recently approved by the US Food and Drug Administration (FDA) for the management of postherpetic neuralgia. This formulation provides gradual release of gabapentin to the optimal site of absorption in the proximal small intestine and reduces the chance of saturating intestinal uptake, thus enabling once-daily dosing of gabapentin. This gradual release and absorption have been demonstrated in pharmacokinetic studies in healthy subjects. The efficacy of once-daily gastroretentive gabapentin for the management of postherpetic neuralgia has been demonstrated in placebo-controlled clinical studies. In addition, data from these studies suggest that the incidence of dizziness and somnolence may be reduced compared with similar studies using gabapentin TID. This article provides an overview of the pharmacokinetics, efficacy, and safety of once-daily gastroretentive gabapentin for the management of postherpetic neuralgia.

Keywords: efficacy, gabapentin, once daily, pharmacokinetics, postherpetic neuralgia, tolerability

Introduction

Herpes zoster affects approximately 1 million people in the USA each year and the lifetime risk of developing the disease is about 30% [CDC, 2011]. Herpes zoster is characterized by a painful, blistering skin rash in one or two dermatomes innervated by a spinal or cranial nerve. Herpes zoster most commonly occurs in older people, with the risk increasing sharply after 50 years of age [CDC, 2011]. Postherpetic neuralgia (PHN) is a condition in which the neuropathic pain persists beyond the clearing of the rash [Dworkin and Portenoy 1996]. As many as 20% of patients with herpes zoster develop PHN and the risk increases with age [Johnson *et al.* 2007]. Although the duration of pain required for a diagnosis of PHN may vary from 1 to 6 months after healing of the rash [Cunningham *et al.* 2000], the rate of

spontaneous remission decreases markedly after 6 months [Oxman *et al.* 2005].

Gabapentin was originally developed and approved as an add-on anticonvulsant drug [Mao and Chen, 2000], but was subsequently shown to be an effective and well tolerated treatment for PHN [Rowbotham *et al.* 1998; Rice and Maton, 2001]. Although the immediate-release formulation of gabapentin [gabapentin TID (three times a day); Neurontin, Pfizer Inc., NY] has been widely used for the management of PHN, there are some drawbacks to its use. Gabapentin is absorbed by a saturable low-capacity L-amino acid transporter expressed predominantly in the proximal small intestine [Stewart *et al.* 1993; Kriel *et al.* 1997] and it has a short elimination half life of 5–7 h [McLean, 1995]. As a result, patients are required

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to take at least three doses per day to maintain therapeutic levels, and frequent dosing may adversely affect patient adherence to treatment [Eisen *et al.* 1990; Claxton *et al.* 2001]. In addition, gabapentin is associated with a high incidence of dizziness and somnolence [Rowbotham *et al.* 1998; Rice and Maton, 2001] that may also effect adherence and prevent patients from achieving a therapeutic dose.

A once-daily gastroretentive formulation of gabapentin (Gralise, Depomed Inc., Menlo Park, CA) has recently been approved by the US Food and Drug Administration (FDA) for the management of PHN. This article reviews the properties of once-daily gastroretentive gabapentin and its demonstrated efficacy and tolerability in the treatment of PHN.

Pharmacokinetics

The pharmacokinetics of gabapentin TID have been described in detail elsewhere [Vollmer *et al.* 1986] and the distribution, metabolism, and excretion of once-daily gastroretentive gabapentin are similar to gabapentin TID. Gabapentin is not appreciably bound to plasma proteins or metabolized and is almost completely eliminated unchanged by renal excretion.

The absorption of once-daily gabapentin is, however, unique because the application of gastroretentive technology has provided a means to address the limitations of gabapentin TID. This gastroretentive technology has also been employed in approved formulations of metformin (Glumetza; Santarus Inc., San Diego, CA, USA). When administered with a meal, the once-daily gabapentin tablet swells upon contact with gastric juices to a size that promotes gastric retention for several hours when taken with a meal [Hou *et al.* 2003; Waterman, 2007]. This gastric retention results in the gradual release of gabapentin to the proximal small intestine at a relatively constant rate over 8–10 h whereas gabapentin TID is completely emptied from the stomach in 30 min. The gradual release of gabapentin from the once-daily gabapentin tablet retained in the stomach extends the time of exposure to the site of absorption in the proximal small intestine and reduces the chance of saturating intestinal uptake. After the drug has been released, the tablet matrix dissolves in about 15 h post dosing [Hou *et al.* 2003; Berner and Cowles, 2006].

Figure 1. Mean (standard error) plasma concentrations of gabapentin following a single 600 mg dose of gabapentin TID ($n = 15$) and once-daily gastroretentive gabapentin ($n = 16$) in healthy volunteers under fed conditions. Adapted from Chen *et al.* [2011], with permission. TID, three times a day.

The pharmacokinetics of gabapentin TID have been compared with the once-daily gastroretentive formulation in several crossover pharmacokinetic studies in healthy volunteers. In the first study, the pharmacokinetics of single 600 mg doses of gabapentin TID and once-daily gastroretentive gabapentin were compared. Following administration of 600 mg of gabapentin TID, peak plasma concentrations occurred at approximately 4 h and then rapidly declined. Following administration of 600 mg of once-daily gastroretentive gabapentin, the time to maximum concentration (T_{max}) was prolonged (to 6 h), the area under the concentration–time curve (AUC) was similar to gabapentin TID, the peak levels were lower, and the decline in plasma gabapentin levels was more gradual (Figure 1) [Chen *et al.* 2011]. The terminal elimination half life, urinary recovery, and renal clearance were similar for once-daily gastroretentive gabapentin and gabapentin TID.

Steady-state pharmacokinetics of once-daily gastroretentive gabapentin were compared with gabapentin TID during daily dosing for up to 8 days [Gordi *et al.* 2008] in a 24-subject three-way crossover study. Subjects received either 1800 mg/day of gastroretentive gabapentin dosed either once daily (QD) (8:00 p.m.) or as an asymmetric divided dose (DD) (600 mg at 8:00 a.m. and 1200 mg at 8:00 p.m.) or gabapentin TID given three times daily (600 mg at 8:00 a.m., 2:00 p.m. and 8:00 p.m.). Plasma concentrations of gabapentin reached a steady state after day 3 of

Table 1. Single-dose and steady-state pharmacokinetic parameters of once-daily gastroretentive gabapentin.

	Gastroretentive gabapentin 1800 mg QD	Gastroretentive gabapentin 1800 mg DD	Gabapentin 1800 mg TID
Day 1			
AUC _{0-∞} (ng/ml h)	123,000 (32,000)	144,000 (29,000)	136,000 (32,000)
C _{max} (ng/ml)	7974 (2157)	6997 (1480)	7455 (1496)
T _{max} (h)	8 [4–12]	20 [16–24]	14 [4–16]
t _{1/2} (h)	7.7 (1.6)	7.1 (1.3)	7.0 (1.0)
Day 8			
AUC ₀₋₂₄ (ng/ml h)	133,000 (35,000)	144,600 (31,000)	141,000 (30,000)
C _{max} (ng/ml)	9585 (2326)	6537 (1216)	8166 (1541)
C _{min} (ng/ml)	1849 (658)	4166 (1335)	3534 (1110)
T _{max} (h)	8 [3–12]	18 [0–24]	8 [2–17]

Adapted from Gordi *et al.* [2008].

Data are mean (standard deviation) except for T_{max}, which are median (range). QD, 1800 mg at 8 p.m.; DD, 600 mg 8 a.m., 1200 mg 8 p.m.; TID, 600 mg 8 a.m., 2 p.m., and 8 p.m.

AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; DD, divided dose; QD, once daily; TID, three times a day; T_{max}, time to maximum concentration; t_{1/2}, half life.

dosing, and the systemic exposure was comparable for all three treatments. When gastroretentive gabapentin was administered QD, the C_{max} was slightly higher and the minimum concentration (C_{min}) was lower compared with gabapentin TID. When gastroretentive gabapentin was given as an asymmetric DD, the C_{max} was slightly lower and the C_{min} slightly higher than with gabapentin TID (Table 1).

The effect of food on the pharmacokinetics of gastroretentive gabapentin QD was examined under fasting, low-fat, and high-fat conditions [Chen *et al.* 2011]. The terminal half life of gabapentin was comparable between fasted and fed subjects, but compared with fasted subjects, the C_{max}, AUC, and T_{max} values were higher in fed subjects and were highest in those fed a high-fat meal. These observations suggest that gabapentin QD tablets are retained longer when taken with food and that the fat content of the food may play an important role in that effect.

Clinical studies with once-daily gastroretentive gabapentin

The efficacy and safety of gastroretentive gabapentin QD have been examined in one phase II and two phase III placebo-controlled studies [Irving *et al.* 2009; Sang *et al.* 2010; Wallace *et al.* 2010]. All studies enrolled patients who had experienced PHN pain for at least 3 months [Irving

et al. 2009; Wallace *et al.* 2010] or at least 6 months [Sang *et al.* 2010] after healing of the herpes zoster skin rash. In all studies, patients were required to have a baseline average daily pain (ADP) score of at least 4, based on an 11-point Likert scale (0 = no pain and 10 = worst possible pain). The primary efficacy endpoint in all studies was the mean change from baseline to the end of the treatment period in ADP score captured in an electronic diary in the morning. In all studies, missing primary endpoint data were imputed using the baseline observation carried forward method.

Efficacy results

In the phase II study, 158 patients with PHN were randomized to 4 weeks of treatment with 1800 mg gastroretentive gabapentin QD (dosed in the evening) or as an asymmetric DD (600 mg a.m., 1200 mg p.m.), or placebo [Irving *et al.* 2009]. Patients were instructed to take gastroretentive gabapentin with a meal and underwent a 2-week dose titration, followed by 2 weeks of stable dosing. Reduction of pain was most evident in the DD group, with a mean change in ADP score of −2.24 compared with −1.93 for the QD group, and −1.29 for the placebo group ($p = 0.014$ and 0.089 for DD and QD groups respectively *versus* placebo). Secondary efficacy outcomes, including sleep interference and the percentage of patients feeling much or

Figure 2. Least squares mean (standard error) change from baseline in average daily pain score with once-daily gastroretentive gabapentin 1800 mg and placebo. * $p < 0.05$ compared with placebo. Adapted from Sang *et al.* [2010], with permission. LS, least squares; SE, standard error.

very much improved on the Patient Global Impression of Change (PGIC), also showed greater improvements in the DD group.

The first phase III study compared QD and DD regimens of 1800 mg/day of gastroretentive gabapentin with placebo in 400 patients. Patients underwent a 2-week dose titration followed by 8 weeks of stable dosing, and 1 week of dose tapering [Wallace *et al.* 2010]. In this study there was an unexpectedly high placebo response and the primary efficacy endpoint was not significantly different between the gabapentin and placebo groups. A *post hoc* analysis showed that the placebo response was especially evident in patients whose rash had healed less than 6 months prior to study entry. However, improvements were observed on most secondary efficacy endpoints, including average daily sleep interference scores and PGIC and Clinician Global Impression of Change (CGIC) scales. Interestingly, in this more rigorous and longer phase III study, these improvements were observed primarily in the QD treatment group. It was concluded that the greater benefit of the DD in the initial phase II study may have been attributable to the shorter duration of that study [Wallace *et al.* 2010].

Given the more promising results with QD dosing in the first phase III study, a second phase III

study was conducted using only the QD dose of 1800 mg [Sang *et al.* 2010]. This study included 452 patients with a PHN duration of at least 6 months. Patients underwent 2 weeks of dose titration, followed by 8 weeks of stable dosing, and 1 week of dose tapering. The mean change from baseline to the end of the efficacy treatment period (week 10) in ADP scores demonstrated a significantly greater reduction for gabapentin QD compared with placebo (-2.12 versus -1.63 ; $p = 0.013$). The between-group difference reached significance at week 1 and continued throughout the study (Figure 2). Patients treated with gastroretentive gabapentin QD in this study also showed greater improvements in sleep interference scores compared with placebo (-2.3 versus -1.6 ; $p < 0.0001$) and a larger percentage of patients taking gastroretentive gabapentin QD felt much or very much improved on the PGIC and CGIC scales compared with patients taking placebo (PGIC: 43% versus 34%, $p = 0.04$; CGIC: 44% versus 34%, $p = 0.03$) [Sang *et al.* 2010].

Adverse events

The types of adverse events reported in clinical trials of gastroretentive gabapentin QD were generally similar to those observed for gabapentin TID. The most commonly reported events were dizziness and somnolence and these were reported

Table 2. Common adverse events reported during phase III studies with gastroretentive gabapentin administered once daily or as a divided dose.

Adverse event	Study 1			Study 2	
	Gabapentin QD (n = 138)	Gabapentin DD (n = 134)	Placebo (n = 133)	Gabapentin QD (n = 221)	Placebo (n = 231)
Dizziness	14 (10)	20 (15)	4 (3)	25 (11)	4 (2)
Headache	5 (4)	9 (7)	6 (5)	10 (4)	9 (4)
Somnolence	4 (3)	9 (7)	3 (2)	12 (5)	7 (3)
Peripheral edema	7 (5)	6 (5)	0	7 (3)	1 (0.4)

From Wallace *et al.* [2010] and Sang *et al.* [2010].
 Adverse events occurring in at least 5% of patients in any treatment group. Data are number (%) of patients. QD, 1800 mg p.m.; DD, 600 mg a.m., 1200 mg p.m.
 DD, divided dose; QD, once daily.

more frequently with gastroretentive gabapentin QD than with placebo in the clinical studies. However, the rates of these key adverse events have been notably modest. In the two phase III studies, among patients who received gastroretentive gabapentin QD, dizziness was reported for 10% of patients in the first study and 11% of patients in the second study and somnolence was reported for 3% of patients in the first study and 5% of patients in the second study (Table 2) [Sang *et al.* 2010; Wallace *et al.* 2010].

Interestingly, in the phase II study, the rates of dizziness and somnolence were lower among patients who received gastroretentive gabapentin DD (dizziness 9%; somnolence 8%) than among those who received QD dosing (dizziness 22%; somnolence 9%) [Irving *et al.* 2009]. However, in the first phase III study, the rates of dizziness and somnolence were slightly higher among patients who received gastroretentive gabapentin DD (15% and 7% respectively) compared with those who received gabapentin QD (10% and 4% respectively) (Table 2) [Wallace *et al.* 2010]. The reasons for this are unclear, but may be related to the different length of the studies (4 weeks and 11 weeks respectively).

Although no direct comparison has been made of gastroretentive gabapentin QD *versus* gabapentin TID, it is notable that consistently higher rates of dizziness and somnolence have been reported in clinical studies with 1800–3600 mg/day gabapentin TID (dizziness 24–33%; somnolence 17–27%) [Rowbotham *et al.* 1998; Rice and Maton, 2001]. One possible explanation for this was suggested in a study of the pharmacokinetics of a gabapentin prodrug, gabapentin enacarbil

[Cundy *et al.* 2008]. In this study, markedly higher gabapentin plasma concentrations were achieved with the prodrug than with gabapentin TID, but the incidences of dizziness and somnolence were similar for both treatments. The authors suggested that these adverse events may be related more closely to the rapid rise in gabapentin levels rather than the absolute concentrations achieved. Thus, it is possible that the more gradual rise in plasma concentration with gastroretentive gabapentin QD helps to mitigate the adverse events of the drug. The lower incidence of these events with gastroretentive gabapentin QD may also be related to the fact that QD dosing in the evening results in peak drug concentrations occurring at night, when the patient is less likely to notice any adverse events. This is supported by the lower incidence of these events among patients who received QD dosing compared with those receiving gastroretentive gabapentin DD (600 mg a.m., 1200 mg p.m.) in the first phase III study, as noted above [Wallace *et al.* 2010].

Other less frequent events reported during treatment with gastroretentive gabapentin QD that were reported for at least 1% of all gabapentin-treated patients and occurred more frequently than in the placebo group included peripheral edema, headache, diarrhea, dry mouth, nasopharyngitis, weight increases, pain in extremity, urinary tract infection, back pain, constipation, vertigo, dyspepsia, pain, and lethargy [Gralise, 2011].

In clinical trials in patients with PHN, 9.7% of the 359 patients treated with gastroretentive gabapentin QD and 6.9% of 364 patients treated with placebo discontinued prematurely due to

Table 3. Recommended titration schedule for once-daily gastroretentive gabapentin.

	Daily dose (mg)
Day 1	300
Day 2	600
Days 3–6	900
Days 7–10	1200
Days 11–14	1500
Day 15	1800

adverse events [Gralise, 2011]. In the gastroretentive gabapentin QD group, the most common reason for discontinuation due to adverse events was dizziness. Interestingly, during the 2-week titration, only 3.6% of patients in the gastroretentive gabapentin QD group and 3% of patients in the placebo group discontinued due to an adverse event (Depomed Inc., Menlo Park, CA, oral communication, data on file), indicating that this titration schedule was well tolerated.

Dosage and administration

Gastroretentive gabapentin QD is available as 300 mg and 600 mg tablets, and like gabapentin TID, should be titrated up to a daily dose of 1800 mg over a period of 15 days (see Table 3). To simplify dose titration, a 30-day starter pack, containing sufficient 300 mg and 600 mg tablets to complete the titration and 2 weeks of stable dosing at 1800 mg per day is available. The tablets should be taken with food and must be swallowed whole, so they should not be split, crushed, or chewed. As with other gabapentin formulations, if gastroretentive gabapentin QD is to be reduced, discontinued, or substituted with an alternative treatment, dosages should be decreased gradually over a period of at least 1 week. Because gabapentin is excreted unchanged via the kidneys, dosing adjustment is required in patients with renal dysfunction and may be necessary in older patients with age-related decline in renal function. For patients with creatinine clearance of 30–60 ml/min, the dose of gastroretentive gabapentin QD should be adjusted to between 600 and 1800 mg/day based on tolerability and desired clinical benefit. Gastroretentive gabapentin QD should not be administered to patients with creatinine clearance less than 30 ml/min or those on hemodialysis. Due to differences in pharmacokinetic properties, gastroretentive gabapentin QD is not interchangeable with gabapentin TID.

Use in specific populations

Because studies of gastroretentive gabapentin QD in specific populations have not been performed, we can only infer from data on gabapentin TID what issues there might be. For example, as noted earlier, dosing may need to be adjusted for patients with renal dysfunction or in older patients with age-related decline in renal function.

Fetotoxicity has been observed with gabapentin TID in animal studies using doses at least three times the maximum recommended dose of gastroretentive gabapentin QD. Therefore, the use of gastroretentive gabapentin QD during pregnancy is only recommended if the potential benefits outweigh the potential risks to the fetus. As gabapentin is also secreted into human breast milk and the effect on nursing infants is unknown, use by nursing mothers is recommended only if the potential benefits outweigh the risks. However, because PHN is a disease observed predominantly in older patients, these recommendations will only apply to a few patients with PHN. The efficacy and safety of gabapentin QD in pediatric patients (<18 years of age) with PHN have not been studied.

Drug interactions

Drug interaction studies of gastroretentive gabapentin QD have not been performed but can reasonably be expected to be the same as those observed with gabapentin TID. Gabapentin has been an attractive treatment option in part due to its lack of significant interactions with most other drugs [Striano and Striano, 2008] as it is not appreciably metabolized and does not inhibit or induce cytochrome P450 enzymes at clinically relevant dosages [Elwes and Binnie, 1996]. Coadministration of gabapentin TID with hydrocodone increases systemic exposure to gabapentin and decreases the exposure to and C_{max} of hydrocodone [Neurontin, 2010]. Gabapentin exposure may also be increased by coadministration of morphine [Eckhardt *et al.* 2000]. The mechanisms underlying these interactions are not known. Aluminum and magnesium-based antacids taken immediately prior to gabapentin TID reduce its bioavailability by about 20%, but only by about 5% if gabapentin TID is taken 2 h after the antacid [Neurontin, 2010]. Therefore, it is recommended that gastroretentive gabapentin QD is taken at least 2 h following antacid administration.

Conclusions

The demonstrated efficacy and tolerability of gabapentin, together with its low propensity for drug–drug interactions, gives it an important place in the treatment of PHN. This latter point is particularly important because PHN predominantly occurs in older patients who often require multiple medications for concomitant conditions. A survey study in the USA found that, among people at least 65 years old, 23% of women and 19% of men reported using at least five prescription drugs within the previous week [Kaufman *et al.* 2002].

Gastroretentive gabapentin QD has the added advantage of less frequent dosing with a longer duration of effect. This feature has the potential to improve treatment adherence because adherence has been found to increase with decreased frequency of dosing [Eisen *et al.* 1990; Claxton *et al.* 2001] and adherence to treatment can impact outcomes in chronic disease [Dimatteo *et al.* 2002]. Furthermore, evening dosing with gastroretentive gabapentin QD may be particularly well suited to address diurnal variation in PHN pain. Patients with PHN usually report progressive worsening of pain throughout the day [Odrich *et al.* 2006]. In general, neuropathic pain is usually reported as worst during the night such that it significantly interferes with sleep [Belgrade, 1999; Schmader, 2002]. Therefore, evening dosing with gastroretentive gabapentin QD would result in maximum exposure during that time when the pain is at its worst and potentially interfering with sleep.

Although the evidence is as of yet only suggestive, gastroretentive gabapentin QD might also have a lower propensity for causing key adverse effects (i.e. dizziness and somnolence) compared with gabapentin TID. This would have obvious advantages with respect to patients' quality of life and might also improve adherence. Further studies will be required to clarify and confirm this important point. However, gastroretentive gabapentin QD is likely to provide a valuable new addition to the physician's armamentarium to treat patients with PHN.

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