

10 OVERDOSSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdose in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences.

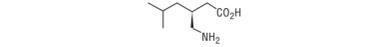
Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observed usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. Contact a Certified Poison Control Center for up-to-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

11 DESCRIPTION

Pregabalin, USP is described chemically as the (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_{11}H_{21}NO_2$ and the molecular weight is 199.23. The chemical structure of pregabalin, USP is



Pregabalin, USP is a white to off-white, crystalline solid with a pK_a of 4.2 and a pK_a of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.35.

Pregabalin capsules are administered orally and are supplied as imprinted, hard gelatin capsules containing 25 mg and 50 mg of pregabalin and the following inactive ingredients: gelatin, iron oxide black, mannitol, potassium hydroxide, pregelatinized starch, propylene glycol, shellac, talc, and titanium dioxide. Additionally, the 50 mg capsules contain DAC yellow #10 and FD&C yellow #6.

12 PHARMACOLOGICAL ACTION

12.1 Mechanism of Action

Pregabalin binds with high affinity to the alpha-2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha-2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest that the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA_A, GABA_B, or benzodiazepine receptors, does not augment GABA_A responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter skin temperature responses to heat in rats. Pregabalin does not block dopamine receptors and does not inhibit dopamine, serotonin, or noradrenergic reuptake.

12.3 Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is greater than or equal to 90% and is independent of dose. Following single- (25 mg to 600 mg) and multiple-dose (75 mg to 600 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with an elimination half-life of 6.7 hours in subjects with normal renal function. Mean renal clearance was estimated to be 63.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CL_{CR}) [see Dosage and Administration (2.7)].

Pharmacokinetics in Specific Populations

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal Impairment and Hemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (CL_{CR}). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified [see Dosage and Administration (2.7)].

Elderly

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CL_{CR}. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function [see Dosage and Administration (2.7)].

Pediatric Pharmacokinetics

Pregabalin clearance is nearly proportional to creatinine clearance (CL_{CR}). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified [see Dosage and Administration (2.7)].

Drug Interactions

In *in vitro* studies, pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. *In vitro* drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of coadministered CYP1A2 substrates (e.g., theophylline, caffeine) or CYP3A4 substrates (e.g., midazolam, testosterone) is not anticipated.

In Vivo Studies
The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin
The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaffected by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive
Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 mcg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine
Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10:11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class

Specific concomitant drug studied

Concomitant drug has no effect on the pharmacokinetics of pregabalin

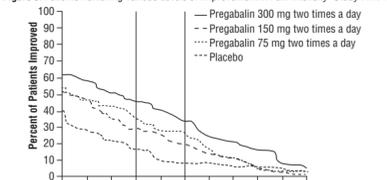
Hypoglycemics

Diuretics

Antiepileptic Drugs

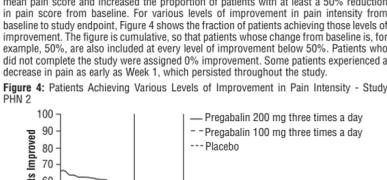
that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 3: Patients Achieving Various Levels of Improvement in Pain Intensity- Study PHN 1



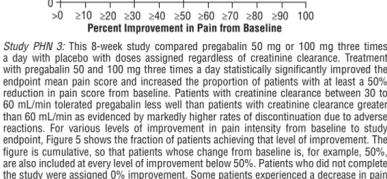
Study PHN 2: This 8-week study compared pregabalin 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with pregabalin statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 4 shows the fraction of patients achieving those levels of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 4: Patients Achieving Various Levels of Improvement in Pain Intensity - Study PHN 2



Study PHN 3: This 8-week study compared pregabalin 50 mg or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with pregabalin 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated pregabalin less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse reactions. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 5: Patients Achieving Various Levels of Improvement in Pain Intensity- Study PHN 3



14 CLINICAL STUDIES

14.1 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The efficacy of the maximum recommended dose of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies with three times a day dosing, two of which studied the maximum recommended dose. Patients were enrolled with either Type 1 or Type 2 diabetes mellitus and a diagnosis of painful distal symmetrical sensorimotor neuropathy. The baseline mean pain scores were established in three 12-week, randomized, multicenter studies in Wistar rats. These findings were observed in plasma pregabalin exposures (AUC) greater than or equal to 2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.