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CHAPTER 59

Perampanel

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Experimental studies in diverse preparations, including brain slices and whole animals, have led to the view that the generation of focal epileptic activity represents an imbalance between synaptic excitation and inhibition. Either a relative excess of excitation or a relative deficiency of inhibition can predispose individuals to the generation of epileptic activity. γ-aminobutyric acid (GABA) is the major neurotransmitter that mediates fast (millisecond time scale) inhibition in the mammalian central nervous system. The earliest antiepileptic agents, including bromide and phenobarbital, as well as newer drugs, including benzodiazepines, tiagabine, and vigabatrin, are believed to act by enhancing the actions of GABA as an inhibitory neurotransmitter. Glutamate is now well accepted as the neurotransmitter that mediates fast synaptic excitation. Neurotransmitter glutamate excites neurons through an action on ionotropic glutamate receptors, which are tetrameric protein complexes localized at synapses. Glutamate released by the presynaptic neuron diffuses across the synaptic cleft, where it encounters glutamate receptors in the postsynaptic membrane. Binding of glutamate causes a conformational change in the receptors so that they transition from the closed (ion impermeant) state to the open (ion conducting) state. Flow of ions through glutamate-bound open receptors generates the excitatory postsynaptic potential (EPSP) as well as the pathologic neuronal excitation that mediates epileptiform discharges in focal epilepsies. It has been recognized since the early 1980s that drugs that inhibit glutamate-mediated excitation can inhibit epileptiform discharges in in vitro systems and can also protect against seizures in animal models (1).

There are three families of ionotropic glutamate receptors, designated *N*-Methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (2). The different families have different roles. Because of the availability of selective pharmacologic blockers, the earliest experimental studies focused on NMDA receptors as a potential antiseizure target. While NMDA receptor antagonists do protect against seizures in some animal models, NMDA receptor antagonists have not proven to be useful in the treatment of epilepsy in humans (3). NMDA receptors make variable, but generally relatively small, contributions to the EPSP and also to the pathologic depolarization that mediates epileptiform discharges in focal epilepsies. The bulk of these electric events is generated in postsynaptic neurons by AMPA receptors. Consequently, blockade of NMDA receptors fails to eliminate epileptiform activity in many in vitro seizure models. In contrast, blockade of AMPA receptors reliably inhibits epileptiform discharges, providing a basis for the use of AMPA receptors in the treatment of epilepsy. Studies with early AMPA receptor antagonists in animal seizure models (4,5) and also the kindling model of epilepsy (6) demonstrated that selective blockade of AMPA receptors could represent a strategy to confer protection against epileptic seizures. These concepts emerged in the 1990s, but it was only with the introduction in 2012 of perampanel, the first AMPA receptor antagonist approved for human use, that AMPA receptors were validated as a human antiseizure target.

Perampanel was discovered around 2000 at the Tsukuba Science City Research Laboratories of the Eisai Company in Ibaraki Prefecture, Japan (7). A precursor molecule was identified by high throughput screening in cell-based in vitro models assessing activity as an AMPA receptor blocker. The core structure of this initial "hit" was modified to improve the potency for inhibition of AMPA receptors and to enhance metabolic stability. A series of analogues were then assessed for in vivo activity in a mouse seizure model in which the test outcome was prolongation of the latency to clonic seizures during constant intracerebroventricular infusion of AMPA. Among a variety of structures with activity in this model, perampanel had the highest in vitro and in vivo potencies. The IC_{50} for inhibition of responses to 1 μM AMPA was 0.06 μM and the minimum effective dose in the mouse AMPA infusion model was 2 mg/kg orally. In studies with human liver microsomes, perampanel was predicted to have a low rate of intrinsic clearance and was later found to have a prolonged duration of action following oral dosing. Pharmacokinetic studies in rats indicated good oral bioavailability and excellent blood–brain barrier penetration. In sum, perampanel is a structurally novel, high potency, orally bioavailable, centrally acting AMPA receptor antagonist with favorable pharmacokintetic properties.

CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND MECHANISM OF ACTION

Chemistry

The International Union of Pure and Applied Chemistry (IUPAC) chemical name for perampanel is 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3). The empirical formula is $C_{23}H_{15}N_3O \bullet ¾\ H_2O$ (MW = 362.90). Perampanel is a white to yellowish white, nonhygroscopic powder. Perampanel exists in different polymorphic or pseudopolymorphic forms, including five anhydrous forms and one hydrate; the drug substance perampanel is controlled as the 3/4 hydrate (Figure 59.1). Perampanel is practically insoluble in water.

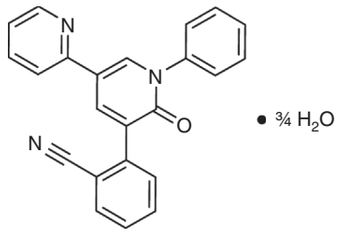

FIGURE 59.1 Structural formula of perampanel.

Preclinical Efficacy Studies

Perampanel has broad spectrum antiseizure activity in animal seizure models, including audiogenic seizures in DBA/2J mice, the maximal electroshock test, the pentylenetetrazol test, and the 6 Hz test (Table 59.1). On the basis of dose, perampanel is among the most potent antiseizure agents known. However, perampanel, as is the case for other AMPA receptor blockers evaluated in animal seizure models (5), caused motor impairment at doses in the range of those conferring seizure protection. The results in the 6 Hz test should therefore be approached with caution as the endpoint is difficult to reliably assess in the presence of neurologic side effects. As has been observed previously for other AMPA receptor antagonists in models of absence seizures (11), perampanel did not have activity in the genetic absence epilepsy rat from Strasbourg (GAERS), an absence seizure model. Whether perampanel can protect against absence seizure in humans remains to be determined.

Preclinical Toxicology Studies

Except where otherwise referenced, data summarized are from the compiled U.S. Food and Drug Administration (FDA) pharmacology reviewer reports of the perampanel new drug application (10).

Acute and Chronic General Toxicology in Adult Animals. Single and repeat-dose toxicology studies were

TABLE 59.1

EFFICACY OF PERAMPANEL IN ANIMAL SEIZURE AND EPILEPSY MODELS

Model	Species (Sex Strain)	Activity
Audiogenic seizure	Mouse (male DBA/2J)	ED_{50} = 0.47 mg/kg, p.o.
Maximal electroshock	Mouse (male ddY)	ED_{50} = 1.6 mg/kg, p.o.
Pentylenetetrazol	Mouse (male ICR)	ED_{50} = 0.94 mg/kg, p.o.
6 Hz	Mouse (male ICR)	ED_{50} = 2.1 mg/kg, p.o. (32 mA) ED_{50} = 2.8 mg/kg, p.o. (44 mA)
GAERS	Rat	No effect on spike-wave discharges at 1, 3, or 10 mg/kg, p.o.
AMPA-induced clonic convulsions	Mouse (ddY)	Effective at 2.5 and 5 mg/kg, p.o.; no effect at 1.25 mg/kg, p.o.
Corneal kindling	Mouse (C57BL/6)	Effective at all doses tested 0.75–3 mg/kg, p.o.
Amygdala kindling	Rat (male Sprague-Dawley, male Wistar Kyoto)	1.5–10 mg/kg increased afterdischarge threshold and decreased motor seizure duration, afterdischarge duration, and seizure severity
Rotarod	Mouse (male ICR)	TD_{50} = 1.8 mg/kg
Rotarod	Rat (male Sprague-Dawley)	TD_{50} = 9.14 mg/kg

Source: From Ref. (8) and Ref. (9) except for GAERS, AMPA-induced clonic convulsions, and corneal kindling, which are from Ref. (10).

performed in mouse, rat, rabbits, dog, and monkey. In male and female mice, decreased activity and abnormal gait was observed with single oral doses of 100 mg/kg and greater. In male and female rats, single oral doses of 10 mg/kg and higher resulted in abnormal gait, prostration, and decreased activity. In female rabbits, abnormal gait and decreased activity were observed with oral doses greater than 10 mg/kg. In male and female beagle dogs, vomiting, abnormal gait, and decreased activity occurred with doses of 1 mg/kg orally. In a male and female cynomolgus monkey, single oral doses greater than 0.3 mg/kg were associated with ataxia, prostration, and drowsiness.

Daily repeat dosing in mice resulted in ataxia and decreased activity, decreased body weight, and excoriation believed to be due to excessive grooming at doses of 10 mg/kg and greater. Mice receiving a daily dose of 30 mg/kg orally lost weight and some animals died. Chronic toxicity studies in rats demonstrated abnormal gait and decreased activity at daily doses of 6 mg/kg orally and greater. The incidence of abnormal gait and decreased activity tended to diminish progressively over 1 to 4 weeks, indicating the development of tolerance. Chronic daily oral dosing in rats for longer than 99 days led to an increase in the incidence of convulsions in relation to controls (although controls were scored as having convulsions on a small percentage of days). The increase in incidence of convulsions occurred at 10 and 30 mg/kg in males and 3 and 10 mg/kg in females; a lower incidence occurred at higher doses, presumably due to the antiseizure effect of the drug. This raises the possibility that long-term exposure to subtherapeutic doses of perampanel may have a risk of convulsions. No consistent organ or histopathologic changes were found. Beagle dogs exhibited vomiting with oral daily doses of 1 mg/kg or more. At a dose of 1 to 3 mg/kg, the dogs exhibited abnormal gait, decreased activity, and prostration. Some dogs exhibited a transitory abnormality in gait at a dose of 0.3 mg/kg. Cynomolgus monkeys receiving perampanel orally once daily for 4 weeks at doses of 0.3 mg/kg exhibited ataxia and decreased activity. Mean C_{max} values at this dose were 83 ng/mL in males and 98 ng/mL in females.

Genotoxicity and Carcinogenicity. No evidence of genotoxicity or carcinogenicity was found with perampanel in studies with Sprague-Dawley (SD) rats and CD-1 mice. However, perampanel was found to be a clastogen but not a mutagen in V79 Chinese hamster cells in the presence of UV irradiation, indicating that it is a photo-clastogen but not a photo-mutagen.

Phototoxicity. In in vitro studies, perampanel was phototoxic to BALB/3T3 cells in the presence of UVA irradiation(IC_{50},0.39 μg/mL) but did not kill the cells in the absence of irradiation. However, in in vivo studies there was no evidence of phototoxicity, contact hypersensitivity, or photoallergy in male hairless guinea pigs.

Acute Effects on Behavior. In male SD rats, a 0.3 mg/kg single oral dose of perampanel was not associated with signs of abnormal behavior, whereas a 1 mg/kg dose caused a minimal change in abdominal tone at 1 and 2 hours after dosing and a 5 mg/kg dose was associated with altered alertness, spontaneous activity, touch response, body position, staggering gait, limb tone, grip strength, body tone, and palpebral opening from 0.5 to 4 hours after dosing.

Reproductive Toxicology. Oral administration of radioactive perampanel (1 mg/kg) as a single dose to pregnant rats is associated with distribution of radioactivity throughout the fetus, indicating that the drug is readily transferred across the placenta. Radioactivity is recovered in the fetal blood, brain, heart, lung, liver, kidney, and digestive track at levels that are a substantial fraction of the levels in the corresponding maternal tissues (typically, 10%–50%). Administration of a single oral dose of radioactive perampanel to lactating rats 4 days postparturition result in levels in milk that are 2.5 to 3.9 times those in plasma during the period 24 hours after dosing. Up to 4 hours following dosing, most of the radioactivity in milk is associated with the parent compound, indicating that unbiotransformed perampanel is excreted in breast milk for at least 4 hours after dosing.

Perampanel at doses up to 30 mg/kg daily in male and female rats for 14 days prior to mating and during mating did not affect fertility, although prolonged and irregular estrous cycles were observed in female rats at 30 mg/kg. Oral daily dosing for 12 days in pregnant rats at doses of 10, 30, and 60 mg/kg was associated with fetal loss and reduced fetal body weight at the 30 and 60 mg/kg doses. Perampanel was found to be teratogenic in SD rats in doses as low as 1 mg/kg. A small number of offspring of pregnant animals receiving oral perampanel on gestation days 6 to 17 exhibited intestinal diverticuli. Pregnant New Zealand white rabbits dosed orally with perampanel at doses of 3 mg/kg and greater on gestational days 6 to 18 had fetal loss.

Developmental Toxicology. SD rat pups born to dams treated orally with perampanel at doses up to 10 mg/kg per day on gestation day 6 to postnatal day 6 were delivered normally and there was no effect on gestation, the number of live offspring at birth, sex ratio, the number of stillbirths, birth or viability measures, or number of external abnormalities, despite the dams exhibiting abnormal gait, decreased activity, and prostration.

Toxicity in Juvenile Animals. Several nonclinical studies in rats and dogs have been conducted to assess the safety of perampanel in pediatric populations. SD rat pups were dosed orally with perampanel for 12 weeks from postnatal day 7 to 90 followed by

a 4-week recovery period. The juvenile rats exhibited reduced activity, incoordination, excessive grooming, and excessive scratching even at a dose of 1 mg/kg/day, the lowest dose tested, and the incidence of these clinical signs increased in a dose-dependent fashion with higher doses. At high doses (titrated up to 30 mg/day), there was reduced growth and body weight, and delayed sexual maturation (preputial separation, vaginal opening). Hindlimb grip strength was reduced during dosing, but this did not persist in the recovery period. Reproductive performance was not affected. Adverse effects of chronic treatment on learning and memory as assessed by the Cincinnati water maze were present but were not dramatic. During dosing, there appeared to be a dose-dependent reduction in learning, particularly at doses of 3 mg/kg and greater; the impact was present but much reduced following discontinuation of drug treatment. C_{max} and $AUC_{0\text{-}24h}$ values associated with the effects on learning were comparable to those expected to be achieved with clinically relevant doses in humans, indicating that persistent effects on learning could occur with chronic treatment. However, it is noteworthy that other AMPA receptor antagonists have generally not been found to impact memory formation or retrieval in animal models even at doses that impair motor function (13). Whether perampanel affects memory function in humans remains to be determined. Nevertheless, it is apparent that juvenile rats are more susceptible to the sedative-like clinical signs and sterotypies of perampanel than are adult rats.

Juvenile dogs dosed daily with oral perampanel for 33 weeks from postnatal day 42 to postnatal week 39 showed incoordination, abnormal gait, altered activity, excessive scratching, and tremors even at doses as low as 1 mg/kg/day, which are associated with C_{max} values of 24 to 99 ng/mL (area under the curve, $AUC_{0\text{-}24h}$: 300–681 ng•h/mL). However, the animals gained weight normally, there was no organ pathology, and their brain measurements were normal with no apparent histopathologic changes (although there was slight ventricular dilation in animals titrated to a dose of 10 mg/kg/day).

Both juvenile rats and juvenile dogs were more susceptible to neurologic toxicity than adult animals. For example, in adult dogs, a daily oral dose of 10 mg/kg, which is associated with C_{max} values of about 130 ng/mL ($AUC_{0\text{-}24h}$: 819 ng•h/mL), caused only abnormal gait, whereas, as noted, this and other toxicities were observed in juvenile dogs at a 10-fold lower dose associated with lower exposures. The results in animals indicate that caution is warranted in the use of perampanel in children and young adults. As discussed later in this chapter, there is evidence from clinical studies that juveniles may be at greater risk for adverse behavioral effects of perampanel than are adults.

Cardiac Safety. Drug-induced prolongation of the QT interval (delay of cardiac repolarization) presents a risk for cardiac arrhythmias, most commonly torsade de pointes, which can be fatal. The potential for QT interval prolongation was assessed with cell-based assays, animal safety studies, a study in healthy volunteers, and in a pooled analysis of data from the Phase III clinical trial program (14). Studies with HEK-293 cells transfected with hERG potassium channels indicate that perampanel inhibits hERG tail current with an IC_{50} of 15.8 μM. In healthy volunteers, the maximum (12 mg) dose of perampanel administered under fasting conditions is associated with perampanel concentrations of less than 1,400 ng/mL (3.9 μM) [mean C_{max} levels <400 ng/mL (1.1 μM)], whereas the maximum concentration observed in the Phase III clinical trials was ~2,500 ng/mL (6.9 μM) (14), providing a margin of safety, particularly in relation to expected free concentrations (4%–5% of total plasma levels). In male and female beagle dogs, a 1 mg/kg single oral dose of perampanel failed to affect mean arterial blood pressure or the electrocardiogram. A dose of 10 mg/kg caused a transitory (4 hours after dosing) increase in heart rate but had no other cardiac effects, including no effect on the QT interval. In healthy male and female human volunteers, oral daily perampanel at doses of 6 and 12 mg did increase the QT interval corrected for heart rate. In the Phase III clinical trials, there was no difference in corrected QT interval between patients with partial seizures treated with placebo and those treated perampanel. Moreover, there was no correlation between plasma perampanel concentrations and QT interval duration with plasma concentrations up to 2,500 ng/mL. Overall, there is no evidence that perampanel presents a clinically relevant risk of QT prolongation.

Preclinical Absorption, Distribution, Metabolism, and Excretion

Perampanel has moderate oral bioavailability in rats (~47%) and dogs (~49%) and higher bioavailability in monkeys (~74%). Plasma protein binding is 94% in mice, 87% in rats, 90% in dogs, and 90% in monkeys. Perampanel mainly binds to albumin and α1-acid glycoprotein and, to a much lesser extent, γ-globulin. It distributes widely throughout the body, including to the fetus of the pregnant rat, and also appears in breast milk (see Toxicology, discussed earlier). Perampanel is rapidly eliminated from the brain, but there is extended residence in various other tissues (up to 106 weeks), including in the eyes of pigmented rats and cynomolgus monkeys, but there is no evidence of ocular toxicity or retinal damage. In rats, but not monkeys, perampanel also appears to exhibit prolonged binding to arteries, but not veins. This unusual observation was not associated

with any histopathologic abnormalities assessed by light microscopy or any evidence of cardiovascular toxicity.

In SD rats, following a single oral dose of radioactive perampanel (1 mg/kg), the radioactivity is completely recovered by 7 days in the feces (88%) with the remainder in the urine (12%). In rats with bile duct cannulae, the radioactivity is completely recovered by 2 days in the bile (92%) and in the urine (7%). In cynomolgus monkeys receiving a single oral dose of radioactive perampanel (0.3 mg/kg), 94% of the radioactivity is recovered by 7 days in the feces (57%) and urine (37%). At this time, no radioactivity is detected in the brain or spinal cord, although there is some radioactivity in the eye as well as in the liver and gallbladder. The metabolic profile of perampanel in rats and monkeys is generally similar to that in humans as discussed subsequently.

Mechanism of Action

Perampanel was first demonstrated to inhibit AMPA receptors using a cell culture assay where changes in intracellular free Ca^{2+} concentration were measured using the fluorescent Ca^{2+} indicator dye fura-2 (8). Exposure of rat cortical neurons to AMPA (2 μM) caused a Ca^{2+} response that was blocked in a concentration-dependent fashion by perampanel with IC_{50} of 0.093 μM. The source of the free Ca^{2+} in these studies is not defined but could relate to entry through various pathways activated by the depolarizing action of AMPA receptor activation (such as voltage-activated Ca^{2+} channels) or to release from intracellular stores. Perampanel was shown more directly to block AMPA receptors in whole-cell voltage-clamp studies in cultured rat hippocampal neurons (15). Perampanel block (IC_{50}, 0.56 μM) was unaffected by the agonist concentration when kainate, a nondesensitizing agonist, was used to activate AMPA receptors, demonstrating a noncompetitive blocking action. AMPA receptor currents exhibit rapid desensitization when activated by the natural agonist glutamate or with AMPA, but perampanel did not alter the time course of the currents. In contrast to its effect on AMPA receptor currents, perampanel had no effect on NMDA receptor currents. Experiments in brain slices have confirmed that perampanel blocks AMPA receptor-mediated synaptic transmission (16). Field EPSPs in hippocampal slices were inhibited with an IC_{50} of 0.23 μM, whereas perampanel did not affect synaptic responses mediated by NMDA or kainate receptors. With chronic daily administration in human patients with epilepsy who are not taking enzyme-inducing concomitant medications, mean perampanel serum concentrations are in the range of 500 ng/mL (1.43 μM) (17). As protein binding is 95%, the unbound concentration is estimated to be about 0.07 μM. If this is taken as an estimate of extracellular concentrations in the brain representing the concentration available at AMPA receptors, it is apparent that in clinical use perampanel only blocks a fraction of AMPA receptors (perhaps <25%). Complete block of AMPA receptors would be incompatible with brain function. However, a degree of partial block seems to be tolerated, although there is clinically relevant protection against seizures.

Studies on Drug-Metabolizing Enzymes

In vitro studies with human liver microsomes have indicated that perampanel (30 μM) does not inhibit cytochrome P450 (CYP) 1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, uridine 5'-diphosphoglucuronosyltransferase (UGT) 1A1, UGT1A4, or UGT1A6 (15). While it is a weak inhibitor of CYP2C8, UGT1A9, and UGT2B7, and possibly CYP3A4, the IC_{50} values are greater than 30 μM, indicating that the inhibitory actions on these enzymes are not clinically relevant. However, studies with recombinant human CYP isoforms indicated that in primary cultured human hepatocytes, perampanel (3 μM but not 0.3 μM or lower concentrations) weakly induces CYP2B6, CYP3A4/5, CYP2B5, UGT1A1, and UGT1A4, but not CYP1A2. The inducing actions are not expected to cause significant drug–drug interactions because the magnitude of the effects are modest, but effects on the pharmacokinetics of drugs that are metabolized by those enzymes that are induced cannot be ruled out.

Studies on Drug Transporter Interactions

Except where otherwise referenced, data summarized in the remainder of this chapter are from the compiled FDA clinical pharmacology reviewer reports of the perampanel new drug application (12).

Various transporters may be involved in the absorption, excretion, distribution, and intracellular concentration of drugs. Actions of a drug at these transporters may influence its pharmacokinetic properties and may play a role in drug–drug interactions. There is no evidence that perampanel interacts with such transporters in a way that is of clinical relevance. Studies with cell lines overexpressing human P-glycoprotein and breast cancer resistance protein indicated that perampanel is not a substrate of either multidrug transporter (18). Perampanel also is not a substrate or inhibitor of OATP1B1 or OATP1B3 transporters; or of organic anion transporters OAT1, OAT2, OAT3; or of organic cation transporters OCT1, OCT2, and OCT3. It does inhibit OAT1, OAT3, OCT1, and OCT3 in a concentration-dependent manner, with OAT3 being the most sensitive (K_i, 8.5 μM). Perampanel stimulated OAT2-mediated transport at concentrations of 1 μM and above. Because the unbound concentration of perampanel is estimated to be much lower than the affinity

values, these transporter interactions are not believed to be clinically relevant.

CLINICAL EFFICACY AND TOLERABILITY

Pivotal Trials

The clinical efficacy and safety of perampanel as adjunctive treatment for focal seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age or older was demonstrated in three Phase III clinical studies encompassing 1,478 patients (19–22). Perampanel administered once daily in doses of 4 to 12 mg/day reduced focal seizure frequency in a dose-dependent fashion. There was also a dose-dependent reduction in the occurrence of secondarily generalized tonic–clonic seizures. In a separate randomized, placebo-controlled study in 164 subjects 12 years of age and older with idiopathic generalized epilepsy who had primary generalized tonic–clonic (PGTC) seizures, there was a statistically significant greater reduction in the frequency of PGTC seizures in the perampanel group (76.5% median reduction) compared to the placebo group (38.4% median reduction) (23). Most of the patients in perampanel group received a daily dose of 8 mg. There was insufficient data to assess the impact of perampanel on generalized seizure types other than PGTC seizures, including myoclonic or absence seizures.

In the Phase III clinical trial program, perampanel was generally well tolerated. The most frequent treatment-emergent adverse events were dizziness, somnolence, fatigue, irritability, nausea, falls, and headache (24). Dizziness, somnolence, and lack of efficacy were the most common reasons for withdrawal. The treatment-emergent adverse effects tended to become evident during the first 6 weeks of treatment; there was no increase in the rate of emergence at later times, even when patients were followed for 1 year in the open-label extension (25). Weight gain was generally more common in perampanel-treated patients than those receiving placebo (26). The average weight gain during the 19-week titration and maintenance phase in the Phase III clinical trials was 1.2 kg in the perampanel group and 0.4 kg in the placebo group. Adolescents, as expected, had overall greater weight gain but the drug effect on weight was less pronounced (perampanel, 1.7 kg; placebo, 1.2 kg) (27). Some weight gain may continue in long-term extension (28). There were no clinically significant changes in vital signs, electrocardiograms, or clinical chemistry, or hematologic values.

Psychiatric side effects have been an issue of concern. In the Phase III clinical trials, depression and aggression were reported more frequently in patients taking perampanel than in patients taking placebo (24,29). The most common psychiatric events in a detailed analysis of the core Phase III trials were irritability, aggression, and anger. The frequency of these adverse events increased in a dose-dependent fashion, as shown in Figure 59.2.

In the Phase III clinical trial, there were three cases of aggression among the perampanel-treated patients that were considered serious and one case of serious suicidal ideation. However, there are anecdotal reports that suggest suicidality may be more frequent. Huber (30) reported three cases of suicidality among 23 adult patients with highly refractory epilepsy. The relationship to the drug treatment was strengthened by the observation that the suicidal thoughts resolved when perampanel was discontinued. In a separate analysis of 47 patients in an epilepsy practice, Coyle et al (31) reported two cases with suicidal ideation.

Pharmacometric analysis of the pooled data from the three Phase III studies indicates that seizure frequency is reduced in a dose- and plasma concentration-dependent manner for doses up to 12 mg per day, which was the highest dose studied in clinical trials (Figure 59.3). There is a corresponding dose- and concentration-dependent increase in the proportion of patients demonstrating hostility and aggression (Figure 59.2).

Concomitant use of enzyme-inducing antiseizure drugs leads to average steady-state levels that are about one-third to one-half those in noninduced patients. This is as expected from the increase in apparent clearance of two-fold to three-fold in induced patients. When subjects are binned into quartiles for steady-state average concentration and the median percentage reduction in seizure frequency is determined for the groups, the concentration–response relationship shown in Figure 59.3 is obtained. Induced and noninduced subjects exhibited a similar concentration–response relationship. However,

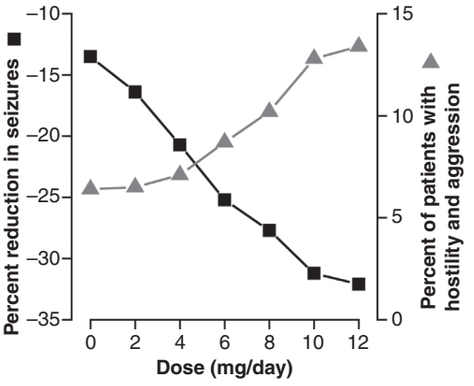

FIGURE 59.2 Predicted percentage reduction in seizure frequency at various daily doses of perampanel compared to the percentage of patients with hostility and aggression adverse events based on data from Phase III clinical trials. The predictions were made based on the median plasma concentration at each dose. The 6 and 10 mg doses were based on simulated exposures.

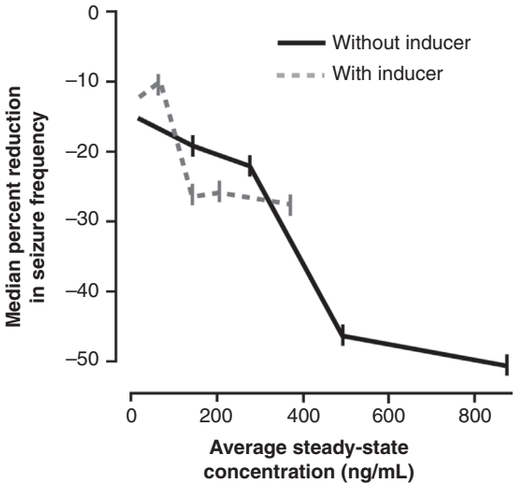

FIGURE 59.3 Median percentage change in seizure frequency in groups of subjects, either noninduced or induced, binned according to the average steady-state plasma concentration quartiles. Vertical lines indicate average steady-state concentration for the quartiles. The concentration of perampanel in patients taking concomitant inducing antiseizure drugs is two-fold to three-fold lower than those who did not. The analysis is based on data obtained in the Phase III clinical trial program.

induced subjects achieved substantially lower serum levels and had a correspondingly less pronounced response. This suggests that induced subjects may benefit from higher doses. To achieve exposures equivalent to those in noninduced subjects and maximal efficacy equivalent to that achieved in noninduced subjects may require doses beyond the 12-mg maximum dose studied in clinical trials (doses up to 15 mg/day have been used) (32).

In long-term follow-up of 1,216 patients in the Phase III trials for up to 3 years (median duration, 1.5 years; 300 patients treated for more than 2 years), the antiseizure response was stable (28). Five percent of patients achieved seizure freedom lasting 1 year or longer. Adverse events were most frequent during dose titration. These included dizziness (46.8%), somnolence (21.2%), and headache (18.3%). Few patients discontinued treatment owing to psychiatric adverse events. However, irritability and aggression were reported in 11.5% and 5.1% of patients, respectively. Other psychiatric side effects reported were depression (5.4%), insomnia (5.3%), anxiety (5.0%), and mood swings (2.1%).

In contrast to the adverse behavioral effects, perampanel treatment has not been associated with specific types of cognitive dysfunction, such as memory impairment or amnesia. Similarly, no disturbance of attention has been noted.

Experience in Children and Adolescents

At the time this chapter was prepared, a controlled study in children ages 2 to 11 was being conducted but the results were not available. The clinical experiences in 58 children and adolescents 2 to 17 years of age with various types of therapy refractory epilepsies has been reported (33). Nearly all of the subjects (90%) were taking one or more concomitant medications. Overall, 31% of subjects exhibited a 50% or more reduction in seizure frequency; 9% achieved complete seizure freedom. The authors noted that children 6 years and older tended to exhibit a better response than younger children, as only 1 of 11 children in the 2 to 5 age group responded. While the numbers are too small to draw conclusions about utility in any specific epilepsy syndrome or seizure type, overall the response rate in generalized epilepsies including Lennox–Gastaut and Dravet syndromes, and generalized seizures, such as absence and myoclonic, were comparable to the response rate in focal seizures. The most frequent adverse events were reduced vigilance or fatigue and behavioral changes, mainly aggressiveness. This is consistent with the results of the Phase III clinical trials where aggressiveness occurred more frequently in younger subjects. Some patients exhibited dizziness, gait instability, or changes in appetite (either loss or gain). No information on dosing in the pediatric population is available.

Subgroup analysis of results for 143 adolescents (ages 12 to 17) in the Phase III clinical trial program showed efficacy that was generally consistent with the efficacy of perampanel in the larger study population (1,480 subjects) consisting mostly of adults (34). In addition, the incidence to specific adverse events in the adolescent population was similar to that of the larger population. Strikingly, however, the incidence of aggression was much greater (22%) than in the overall population (4.5%).

In a separate study in adolescents (12 to 17 years of age) randomized to perampanel (target dose 8 to 12 mg/day; n = 85) or placebo (n = 48), the active drug did not demonstrate a detrimental impact on standardized measures of behavior as assessed with the Child Behavior Checklist (35). Nevertheless, more patients in the perampanel group exhibited aggression (8.2%) than in the placebo group (2.1%).

ABSORPTION, BIOTRANSFORMATION, PHARMACOKINETICS, AND INTERACTIONS IN HUMANS

Absorption and Distribution

Perampanel is rapidly absorbed after oral administration. Under fasted conditions, the median T_{max} ranges from 0.5 to 2.5 hours after single or multiple dose administration. Dosing with a high fat meal reduced the C_{max} by 28% to 40% and delayed the T_{max} by 2

to 3 hours, but did not affect the exposures (AUC). Therefore, perampanel can be taken with or without food. The volume of distribution (Vd) in healthy volunteers ranges from 51 to 105 L (average, 77 L, or about 1.1 L/kg in a 70-kg subject). The Vd value indicates that perampanel distributes to both extracellular and intracellular fluid. Perampanel exhibits dose-proportional pharmacokinetics such that the peak plasma concentration (C_{max}) and exposure (AUC) after single and multiple doses increase in a linear fashion with doses in the range of 1 to 12 mg, except that the C_{max} increased less than the dose proportionally beyond a dose of 8 mg (36). With once-daily dosing, steady-state plasma levels are achieved at about day 14. The $AUC_{0\text{-}24hr}$ after 14 days of once daily dosing is 4.1 times that of the $AUC_{0\text{-}24hr}$ on the first day. In humans, perampanel has plasma protein binding of 95% to 96%.

Metabolism and Elimination

Perampanel is extensively metabolized, primarily by CYP3A4 followed by glucuronidation. Unchanged perampanel accounts for 75% to 80% of the total drug-related material in plasma. No major metabolite is present in the systemic circulation. Therefore, although some metabolites act as AMPA receptor blockers, the contribution of metabolites to the pharmacodynamic effect is believed to be negligible. Only small amounts of the parent drug are present in the feces due to high oral bioavailability and extensive metabolism. Less than 0.2% of the unchanged drug is recovered in the urine. Oral clearance (CL/F) is similar in healthy subjects and patients with focal seizures (see Table 59.2). Oral clearance is 17% less in females than males (Table 59.2) (37). The terminal elimination half-life ($t_{½}$) is approximately 105 hours based on a population pharmacokinetic analysis of data obtained in healthy volunteers.

Drug–Drug Interactions

Because the metabolism of perampanel is largely via CYP3A4 in the liver, the clearance is influenced by concomitant enzyme-inducing antiseizure drugs. The most significant interactions between perampanel and other

TABLE 59.2

PERAMPANEL CLINICAL PHARMACOKINETIC PROFILE

Parameter	Value/Comment
Absorption	• Oral bioavailability: 100% • Food effect: rate of absorption decreased but no change in exposure
Pharmacokinetic Parameters T_{max} C_{max} (1 mg single oral dose) $AUC_{0\text{-}\infty}$ (1 mg single oral dose) Dose linearity Plasma-protein binding V_d Time to steady state with daily dosing	• 0.5–1 hours (fasted), 3 hours (fed) • 35 ng/mL (fasted), 21 ng/mL (fed); steady-state C_{max} 2.5-fold • 1,320 ng•hr/mL • Linear (C_{max} and AUC increase in dose-proportional manner up to 8 mg) • 95%–96% • 77 L (51–105 L) • 14 days
Metabolism	• Oxidation primarily by CYP3A4 in liver (98%) followed by glucuronidation • Weak induction • Minimal renal (<0.2%) excretion of unchanged perampanel
Elimination Terminal $t_{½}$ Oral clearance (CL/F)	• In healthy volunteers: single dose: 51–129 hours (mean, 105 h); multiple dose: 66–90 h. In the presence of inducing comedications, 25 h • Without significant antiseizure drug[a]: 0.730 L/h (adult males); 0.605 L/h (adult females); 0.787 L/h (adolescent) • With carbamazepine: 2.016 L/h (adult males); 1.891 L/h (adult females); 2.322 L/h (adolescent) • With oxcarbazepine: 1.377 L/h (adult males); 1.253 L/h (adult females); 1.629 L/h (adolescent) • With phenytoin: 1.455 L/h (adult males); 1.330 L/h (adult females) • With topiramate: 0.905 L/h (adult males); 0.781 L/h (adult females)

Note: Based upon single and multiple dose studies in healthy adult subjects (12,37).
[a]Significant antiseizure drugs are carbamazepine, oxcarbazepine, phenytoin, and topiramate.

antiseizure medications is the effect of inducing drugs such as carbmazepine, oxcarbazepine, and phenytoin, which increase perampanel clearance, thus reducing exposures. Concomitant carbamazepine caused about a three fold increase in perampanel clearance, whereas oxcarbazepine and phenytoin caused about a two-fold increase (Table 59.2), causing exposures to one-third and one-half, respectively, of that in patients not taking inducing drugs. Concomitant topiramate was associated with a smaller increase in perampanel clearance that may not be as clinically significant. No increase in perampanel clearance was noted with clobazam, clonazepam, lamotrigine, levetiracetam, phenobarbital, primidone, valproate, and zonisamide. CYP3A4 inhibitors are expected to increase levels of perampanel. For example, in a study in healthy male volunteers, ketoconazole, a strong inhibitor of CYP3A4, was found to increase perampanel exposure levels by 20% and $t_{½}$ by approximately 15% (17). Little is known about the effects of perampanel on other types of drugs.

In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day, perampanel did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. Perampanel had a significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the magnitude of these effects was less than 10% for each drug at the highest perampanel dose evaluated (12 mg/day). Perampanel coadministration resulted in a 26% decrease in oxcarbazepine clearance, resulting in increased plasma levels.

Studies have been conducted in healthy premenopausal females to assess the interaction of perampanel with an oral contraceptive containing 30 μg ethinylestradiol and 150 μg levonorgestrel. Subjects receiving 12 mg perampanel daily exhibited a 42% and 40% decrease in levonorgestrel C_{max} and $AUC_{0\text{-}24h}$, respectively, and an 18% decrease in ethinylestradiol C_{max} without affecting its $AUC_{0\text{-}24h}$. Lower doses of perampanel did not signifi cantly alter the pharmacokinetic properties of the steroids. It is concluded that administration of daily perampanel at a dose of 12 mg may decrease the effectiveness of levonorgestrel-containing hormonal contraceptives. Three-week consecutive administration of the oral contraceptive did not affect the pharmacokinetic properties of a 6 mg dose of perampanel, indicating that oral contraceptives are unlikely to influence perampanel effectiveness.

Use in Special Populations

Renal clearance is a minor route of elimination. Nevertheless, population pharmacokinetic analysis using data from the Phase III clinical trials indicated that median perampanel clearance was 27% lower in patients with mild renal impairment [creatinine clearance (CL_{cr}), 50–80 L/hr)] compared to patients with normal renal function (CL_{cr} >80 L/hr), resulting in higher perampanel exposure. The extent of the increase in exposure was not of sufficient magnitude to prompt a recommendation for dose adjustment (17). Only three patients with moderate renal failure (CLcr, 30–50 L/hr) were included in the Phase III clinical trials; the median perampanel clearance was similar to that of patients with mild renal failure. Based on this limited data, it is recommended that perampanel may be used in patients with moderate renal failure but with close monitoring. Because the effects of severe renal impairment and end-stage renal disease cannot be predicted, use in these patients is not recommended.

Perampanel pharmacokinetics has been studied in subjects with hepatic impairment. In mild hepatic impairment (Child-Pugh A) there was an increase in exposure of 49% and the terminal $t_{½}$ was prolonged from 125 hours in demographically matched healthy volunteers to 306 h. In patients with moderated hepatic impairment (Child-Pugh B), there was an increase in exposure of 155% and $t_{½}$ was prolonged from 139 to 295 hours. Due to decreased plasma protein binding in hepatically impaired patients, the unbound fraction of perampanel was 27% and 73% higher in mild and moderate hepatic impaired patients compared to control subjects, and the exposure ($AUC_{0\text{-}inf}$) of free perampanel is 1.81-fold and 3.28-fold, respectively. It is recommended that the perampanel dose not exceed 6 mg and 4 mg, respectively, in mild and moderate hepatic impairment. Due to the prolonged $t_{½}$, patients with mild or moderate hepatic impairment should be dose titrated more slowly with close monitoring to avoid overdosing.

Pediatric Pharmacokinetics

No pharmacokinetic information is available in children younger than 12 years of age. Population pharmacokinetic analyses from the pooled data in adolescents in the Phase III efficacy trials showed that adolescent patients (ages 12 to 17 years) had slightly higher clearance than adult patients, but the magnitude of this difference is not considered to be clinically meaningful (Table 59.2). Similar effects of concomitant carbamazepine and oxcarbazepine on perampanel clearance were observed in adolescents as in adult patients.

Table 59.3 compares mean perampanel concentration values in all subjects in the Phase III clinical trials with those for all adolescent patients and the subgroup taking concomitant carbamazepine. There were no consistent differences in blood levels in adolescents compared to the entire study population.

TABLE 59.3

STEADY-STATE PERAMPANEL PLASMA CONCENTRATIONS IN ADOLESCENTS 12 TO 17 YEARS OF AGE WITH PHARMACORESISTANT FOCAL SEIZURES IN THE PHASE III CLINICAL TRIALS COMPARED TO VALUES FOR ALL PATIENTS				
Daily Dose (mg)	**All Patients**	**All Patients Except Those Receiving EIASDs**	**All Adolescents**	**Adolescents Taking Concomitant Carbamazepine**
	Mean Perampanel Plasma Concentration (ng/mL)			
2	71	157.2	57.4	34.7
4	138	389.0	109.6	55.3
8	272	648.1	277.1	131.2
12	349	907.4	278.0	231.1

Note: EIASD, enzyme-inducing antiseizure drug. Population pharmacokinetic analyses from Phase III studies. All patients data from FDA Medical Review (44). All patients except those receiving EIASDs from Kwan et al (38). Adolescent data from Rosenfeld et al (34).

CLINICAL USE

Perampanel is formulated as immediate release tablets, which are manufactured in six different dosage strengths: 2, 4, 6, 8, 10, and 12 mg. The availability of multiple strengths allows patients to take a single tablet regardless of dose. Statistical analysis of the Phase III efficacy data indicates that 4 mg once daily is the minimum effective dose, but some clinicians have reported efficacy with even the 2 mg dose. A typical maintenance dose for patients 12 years of age and older is 4, 6, or 8 mg per day. Higher doses may be needed in patients who are receiving CYP3A4-inducing comedications such as carbamazepine, oxcarbazepine, or phenytoin. There are anecdotal reports of seizure freedom in difficult-to-treat patients with perampanel doses as low as 4 or 6 mg per day, even when taking enzyme-inducing concomitant antiseizure drugs (39,40). Apart from pharmacokinetic interactions, there is no evidence that use of perampanel in combination with any other antiseizure drug is more or less preferred (38). While some sodium channel-blocking antiseizure drugs may require higher perampanel doses because of CYP3A4 induction, no dose adjustment is required with concomitant use of noninducing sodium channel-blocking drugs such as lacosamide, lamotrigine, and rufinamide. Specific dosing recommendations for patients younger than 12 years of age are not available. Dosing is generally based on individual clinical response and tolerability. In adolescents (34) and in the larger clinical study (27), there was greater effectiveness at doses above 8 mg per day; however, some patients may not tolerate these higher doses. Other patients, however, only achieve the best possible therapeutic response at doses of 10 or 12 mg per day (41). The 12 mg dose may be particularly problematic owing to adverse events and is generally reserved for patients taking concomitant medications that reduce perampanel exposures. Although there is very limited information on the use of doses greater than 12 mg per day (40), the pharmacokinetic data suggest that in some induced patients higher doses may be required to achieve exposures equivalent to those in noninduced subjects.

Perampanel use has been associated with adverse behavioral effects, variously described as aggression, hostility, irritability, anger, and homicidal ideation and threats. These symptoms occur more frequently in younger patients. Therefore, patients and their caregivers should be alerted to the potential for aggressive behaviors. Particular care has been suggested for patients with learning disability or dementia (42). Alcohol use may exacerbate the level of anger.

In the Phase III clinical trials, the percentage reduction in seizure frequency increased in a dose- and concentration-dependent manner. However, the proportion of patients exhibiting side effects, including hostility and aggression, also increased with dose. Therefore, it is advisable to up-titrate slowly and stop increasing the dosage when the desired therapeutic response is obtained. The recommended starting dosage is 2 mg once daily and it is recommended that the dose be increased in increments of 2 mg once daily no more frequently than at weekly intervals. Most experienced clinicians increase the dose no more frequently than at 2-week intervals because steady-state plasma levels are not achieved at shorter times. Slow titration avoids overshooting the minimally effective dose. In addition, slower titration may decrease the incidence or severity of some adverse effects. In adolescents, it may be prudent to titrate even more slowly, increasing the dose only every 2 to 3 weeks (42). The experience in the open-label extension is that

with a 2-week titration schedule most patients are able to reach 10 mg per day and only 4% discontinue owing to adverse events (28). Because of the tendency to produce sedation, administration at bedtime is advised (39). Some clinicians have found that dividing the dose is beneficial. Although the average exposure is equivalent to once daily dosing, twice daily dosing results in reduced peak to trough fluctuations (43). In the absence of enzyme-inducing antiseizure drugs, the difference is modest. However, when concomitant enzyme-inducing antiseizure drugs are present, the peak-to-trough fluctuations can be quite large; this is reduced by twice-a-day dosing (43). In healthy volunteer studies, dosing with a high-fat breakfast caused a 39% reduction in C_{max} and increase in t_{max} from 1 to 3 hours. However, the mean exposure ($AUC_{0-\infty}$) was unchanged. Therefore, perampanel may be administered with or without food. The long $t_{½}$ of perampanel (~105 h) allows once daily dosing, which is convenient for patients and is believed to improve adherence (43). Fluctuations in plasma concentration during the day are more modest than with drugs that have shorter $t_{½}$ value, thus reducing the likelihood of underexposure, which may lead to seizures, or overexposure and resulting side effects. In patients receiving concomitant enzyme-inducing antiseizure drugs, simulations have shown that the longer $t_{½}$ results in greater "forgiveness" in the event of a missed dose. Missing a dose is expected to lead to no more than a 20% reduction in trough blood concentrations. Replacing the missed dose would not markedly infl uence the drug exposure, leading to the recommendation that replacement is not necessary and patients should simply take the next scheduled daily dose. Because clearance is greater in the presence of enzyme-inducing antiseizure drugs, missing a dose has greater impact on blood concentrations so that replacement dosing is warranted in this situation to mitigate the potential risks of reduced exposure.

Perampanel is also available as a liquid oral suspension (0.5 mg/mL) that can be used interchangeably with the tablets as it has comparable bioavailability.

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