

'On-Off' Switches Shed Light on Brain Disorders

Narcolepsy, cataplexy, and REM sleep behavior disorder linked to errant 'flip-flop' mechanisms.

BY BETSY BATES

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE AMERICAN NEUROLOGICAL ASSOCIATION

SAN DIEGO – A series of “on-off” switches regulates sleep, clarifying many

of the mechanisms underlying narcolepsy, cataplexy, and REM sleep behavior disorder, according to Dr. Clifford B. Saper.

The states of sleep and wakefulness and rapid eye movement and non-REM sleep can best be understood as “flip-flop” mechanisms of brain circuitry, akin

to light switches, said Dr. Saper, professor of neurology and neuroscience at Harvard Medical School and head of the department of neurology at Beth Israel Deaconess Medical Center in Boston.

“Each side inhibits the other” in an ascending arousal pathway to the cortex, facilitating rapid transitions from one state to the other.

Normally, human beings spend 99% of the 24-hour day fully awake or fully

asleep, and just 1% of the time transitioning. This is due to an on-off switch that regulates arousal and sleep, Dr. Saper said at the meeting.

“One of the problems with a flip-flop switch is that it has a tendency, sometimes, to fall into the wrong position too easily. One can imagine driving down a boring road and flipping into the wrong state and suddenly being asleep behind the wheel of a car,” he said.

To prevent such an occurrence, the brain stabilizes wakefulness by the use of orexins, or hypocretins, which are neuropeptides produced by excitatory neurons in the lateral region of the hypothalamus.

Narcolepsy, in which patients do fall asleep essentially at the “flip of a

Lacosamide has been shown *in vitro* to interfere with the activity of collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axonal outgrowth. Potential adverse effects on CNS development can not be ruled out.

There are no adequate and well-controlled studies in pregnant women. VIMPAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of lacosamide to pregnant rats (20, 75, or 200 mg/kg/day) and rabbits (6.25, 12.5, or 25 mg/kg/day) during the period of organogenesis did not produce any teratogenic effects. However, the maximum doses evaluated were limited by maternal toxicity in both species and embryofetal death in rats. These doses were associated with maternal plasma lacosamide exposures [area under the plasma-time concentration curve; (AUC)] \approx 2 and 1 times (rat and rabbit, respectively) that in humans at the maximum recommended human dose (MRHD) of 400 mg/day.

When lacosamide (25, 70, or 200 mg/kg/day) was orally administered to rats throughout gestation, parturition, and lactation, increased perinatal mortality and decreased body weights were observed in the offspring at the highest dose. The no-effect dose for pre- and post-natal developmental toxicity in rats (70 mg/kg/day) was associated with a maternal plasma lacosamide AUC approximately equal to that in humans at the MRHD.

Oral administration of lacosamide (30, 90, or 180 mg/kg/day) to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide AUC approximately 0.5 times that in humans at the MRHD.

Pregnancy Registry

UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with VIMPAT. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling 1-888-537-7734 (toll free).

Physicians are also advised to recommend that pregnant patients taking VIMPAT enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

Labor and Delivery

The effects of VIMPAT on labor and delivery in pregnant women are unknown. In a pre- and post-natal study in rats, there was a tendency for prolonged gestation in all lacosamide treated groups at plasma exposures (AUC) at or below the plasma AUC in humans at the maximum recommended human dose of 400 mg/day.

Nursing Mothers

Studies in lactating rats have shown that lacosamide and/or its metabolites are excreted in milk. It is not known whether VIMPAT is excreted in human milk. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue VIMPAT, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of VIMPAT in pediatric patients <17 years have not been established.

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Geriatric Use

There were insufficient numbers of elderly patients enrolled in partial-onset seizure trials (n=18) to adequately assess the effectiveness of VIMPAT in this population.

In healthy subjects, the dose and body weight normalized pharmacokinetic parameters AUC and C_{max} were approximately 20% higher in elderly subjects compared to young subjects. The slightly higher lacosamide plasma concentrations

in elderly subjects are possibly caused by differences in total body water (lean body weight) and age-associated decreased renal clearance. No VIMPAT dose adjustment based on age is considered necessary. Caution should be exercised for dose titration in elderly patients.

Patients with Renal Impairment

A maximum dose of 300 mg/day is recommended for patients with severe renal impairment (CL_{CR} \leq 30 mL/min) and in patients with endstage renal disease. VIMPAT is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, AUC of VIMPAT is reduced by approximately 50%. Therefore dosage supplementation of up to 50% following hemodialysis should be considered. In all renal impaired patients, the dose titration should be performed with caution. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information]

Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment should be observed closely during dose titration. A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment. VIMPAT use is not recommended in patients with severe hepatic impairment [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information]. Patients with co-existing hepatic and renal impairment should be monitored closely during dose titration.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

VIMPAT is a Schedule V controlled substance.

Abuse

In a human abuse potential study, single doses of 200 mg and 800 mg lacosamide produced euphoria-type subjective responses that differentiated statistically from placebo; at 800 mg, these euphoria-type responses were statistically indistinguishable from those produced by alprazolam, a Schedule IV drug. The duration of the euphoria-type responses following lacosamide was less than that following alprazolam. A high rate of euphoria was also reported as an adverse event in the human abuse potential study following single doses of 800 mg lacosamide (15% [5/34]) compared to placebo (0%) and in two pharmacokinetic studies following single and multiple doses of 300-800 mg lacosamide (ranging from 6% [2/33] to 25% [3/12]) compared to placebo (0%). However, the rate of euphoria reported as an adverse event in the VIMPAT development program at therapeutic doses was less than 1%.

Dependence

Abrupt termination of lacosamide in clinical trials with diabetic neuropathic pain patients produced no signs or symptoms that are associated with a withdrawal syndrome indicative of physical dependence. However, psychological dependence cannot be excluded due to the ability of lacosamide to produce euphoria-type adverse events in humans.

OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans

There is limited clinical experience with VIMPAT overdose in humans. The highest reported accidental overdose of VIMPAT during clinical development was 1200 mg/day which was non-fatal. The types of adverse events experienced by patients exposed to supratherapeutic doses during the trials were not clinically different from those of patients administered recommended doses of VIMPAT.

There has been a single case of intentional overdose by a patient who self-administered 12 grams VIMPAT along with large doses of zonisamide, topiramate, and gabapentin. The patient presented in a coma and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later.

Treatment or Management of Overdose

There is no specific antidote for overdose with VIMPAT. Standard decontamination procedures should be followed. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with VIMPAT.

Standard hemodialysis procedures result in significant clearance of VIMPAT (reduction of systemic exposure by 50% in 4 hours). Hemodialysis has not been performed in the few known cases of overdose, but may be indicated based on the patient's clinical state or in patients with significant renal impairment.

PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide and Patient Counseling Information section in the Full Prescribing Information.



The flip-flop switch 'has a tendency, sometimes, to fall into the wrong position too easily.'

DR. SAPER

switch,” is the result of a single neurotransmitter deficit in sleep’s “master switch,” the ventrolateral preoptic nucleus, Dr. Saper explained.

A similar “flip-flop” switch regulates the normally rapid transition between REM and non-REM (slow-wave) sleep, he said.

The development of REM sleep behavior disorder (in which patients make jerky motor maneuvers as they act out dreams during sleep) and cataplexy – atonic lapses in muscle control from a waking state – are opposites on a spectrum, both indicative of triggering of the on-off mechanism at an inappropriate point in the cycle.

Of great interest to Dr. Saper is an evolving apparent link between the development of REM sleep behavior disorder in young adulthood and later development of Parkinson’s disease, a phenomenon that occurs in about half of REM behavior disorder patients within 12 years.

He noted that Dr. Ronald B. Postuma and his associates at Montreal General Hospital have identified early markers of Parkinson’s disease in idiopathic REM sleep behavior disorder patients, including difficulties with visual and olfactory discrimination tasks and subthreshold but low scores on the Unified Parkinson’s Disease Rating Scale.

The connection has led some researchers to suspect that synucleinopathies such as Parkinson’s disease and dementia with Lewy bodies may begin at the brainstem level of the locus coeruleus or the subcoeruleus complex and slowly progress in an ascending pathway to the basal ganglia over years or decades, offering the possibility of introducing neuroprotective therapy to stop that progression.

Dr. Saper reported having no relevant financial disclosures. ■

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