Losing sleep over flumazenil

By Lauren Martz, Staff Writer

Emory University School of Medicine researchers have identified excessive daytime sleepiness as a repurposing opportunity for flumazenil, a generic GABA_A receptor antagonist.¹ Although safety issues have stymied prior attempts to use GABA_A receptor antagonists in this chronic indication, the group thinks a new formulation could make it possible.

Flumazenil is the only FDA-approved GABA_A antagonist. It is a competitive antagonist that targets the benzodiazepine binding site on GABA_A receptors and is marketed to treat sedative overdose and improve recovery from anesthesia.

Previous studies have shown that flumazenil increases vigilance in patients with sleep deprivation, idiopathic recurrent stupor and hepatic encephalopathy.²⁻⁴ However, the drug's side effects include anxiety and seizures. Those adverse events plus the short-lived activity of the drug have discouraged its development for sleep disorders.

Nevertheless, David Rye and colleagues at Emory set out to determine whether flumazenil could reverse the excessive GABA_A receptor activity that might underlie conditions including idiopathic hypersomnia and narcolepsy without cataplexy. Both are types of excessive daytime sleepiness for which existing therapeutics are ineffective.

Rye is a professor of neurology at Emory University School of Medicine and director of research at **Emory Healthcare's** Program in Sleep Medicine.

To confirm that GABA_A activity was elevated in the CNS of patients with hypersomnia, Rye's team cultured human embryonic kidney cells expressing γ -aminobutyric acid (GABA) family receptors in the presence of cerebrospinal fluid (CSF) from hypersomnolent patients plus 10 μ M exogenous GABA_A.

The combination of GABA_A plus CSF from patients increased GABA_A signaling more than GABA_A alone or GABA_A plus CSF from healthy controls. In the same cells, flumazenil reversed the effects of patient CSF on GABA_A signaling.

Next, Rye and colleagues treated seven hypersomnia patients with a single injection of saline plus flumazenil. The patients showed improved vigilance and subjective alertness following treatment.

Finally, the team looked at whether flumazenil had long-term efficacy. Due to the short half-life of injectable flumazenil, they generated sublingual and transdermal formulations of the drug. In a single patient

with idiopathic hypersomnia, the new formulations given every two to three hours while the patient was awake reduced excessive daytime sleepiness over four years.

Rye told *SciBX* that "the next steps include conducting a larger, double-blind, placebo-controlled trial." Details of the trial are not yet decided, he said, but the study likely would be run by **Emory University** or as part of the **National Institute of Neurological Disorders and Stroke's** Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) consortium. The trial is planned for the fall of 2013 at the earliest.

Results were published in *Science Translational Medicine*.

Path to repurposing

Although the findings point to the potential to repurpose flumazenil, the clinically approved version of the compound is intravenous, short lived and intended for single-injection applications. Moreover, the drug carries a black box warning of seizure risk.

"Flumazenil has limited value to these patients because it has a short half-life and rapid metabolism," said Bjarke Ebert, senior medical advisor at **H. Lundbeck A/S**.

Thus, he said, the Emory researchers "need to confirm that their sublingual version and transdermal formulation lead to a steady-state blockade of the benzodiazepine site."

Lundbeck markets Tranxene clorazepate dipotassium, an oral benzodiazepine, to treat anxiety disorders.

"It might be worth seeking compounds with the same mechanism as flumazenil that are longer acting," suggested Karl-Uwe Petersen, VP of preclinical development at **Paion AG's** Paion

Deutschland GmbH subsidiary.

Rye said his team is considering screening for new compounds with the same mechanism of action. "Ideally, discovering more details about the pharmacological targets could allow probing from additional molecular libraries for alternative promising treatments," he said.

Paion and **Ono Pharmaceutical Co. Ltd.** have completed Phase II testing of Remimazolam, a short-acting general anesthetic and sedative that activates the GABA_A receptor.

On the safety front, seizure risk could be addressed with a dose-escalation trial of flumazenil with continuous electroencephalography or brain imaging surrogate endpoints, said Matt Bianchi, assistant professor of neurology in the Sleep Division at **Massachusetts General Hospital**.

Despite the safety hurdles, flumazenil could have an advantage over other hypersomnia therapeutics because it targets the pathological mechanisms that underlie the condition.

"The issue with current stimulatory agents is that they are not useful in all subjects, and they do not directly address the problem that has been identified in the types of hypersomnia patients described in the paper," said Petersen.

He added, "The difference between GABA_A modulators and existing strategies to treat daytime sleepiness is that most therapies are aimed at increasing excitation, while GABA_A modulators are aimed at reducing the

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**—David Rye,
Emory University
School of Medicine**

dampening effect on excitation. The problem with excitatory stimulation is that it is not a very direct method. It really just increases consciousness and requires high doses that could lead to side effects. For example, the widely used modafinil can cause headaches, changes in blood pressure and overstimulation that can cause nervousness and sleeplessness.”

Teva Pharmaceutical Industries Ltd. markets Provigil modafinil to treat narcolepsy, shift work sleep disorder and excessive sleepiness associated with obstructive sleep apnea.

Ebert added, “It is clear that modafinil works for a lot of patients with excessive daytime sleepiness, but it is not exactly clear how. For flumazenil, we have the mechanism of action, and it appears that the drug might actually address the pathophysiology of the disease.”

Rye said that although it is hard to compare the efficacy of drugs across different types of hypersomnias, his team found that flumazenil improved vigilance in patients with sleepiness attributed to shift work. In 2005, a group from **Harvard Medical School** and **Cephalon Inc.** found a smaller impact of modafinil on vigilance in patients with the same condition.⁵

Emory University has patented the work, and the IP is unlicensed.

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e-mail: drye@emory.edu
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COMPANIES AND INSTITUTIONS MENTIONED

Cephalon Inc. (NASDAQ:CEPH), Frazer, Pa.
Emory Healthcare, Atlanta, Ga.
Emory University, Atlanta, Ga.
Emory University School of Medicine, Atlanta, Ga.
Harvard Medical School, Boston, Mass.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Massachusetts General Hospital, Boston, Mass.
National Institute of Neurological Disorders and Stroke, Bethesda, Md.
Ono Pharmaceutical Co. Ltd. (Tokyo:4528; Osaka:4528), Osaka, Japan
Paion AG (Xetra:PA8), Aachen, Germany
Teva Pharmaceutical Industries Ltd. (NYSE:TEVA), Petah Tikva, Israel