Inhaled Thyrotropin-Releasing Hormone for Treatment of Neuropsychiatric Disorders

To the Editors:

Thyrotropin-releasing hormone (TRH) displays multiple central nervous system–mediated actions that have therapeutic potential in treating a wide range of neuropsychiatric disorders. Investigations of central nervous system functions and clinical use of TRH are hindered, however, because of its rapid degradation by circulating peptidases.[1] To circumvent this problem, Veronesi et al[2] have developed an intranasal nanoparticle drug delivery system. Thyrotropin-releasing hormone could be introduced into the nasal cavity, where the olfactory neurons can collect particles directly. The TRH incorporated into biodegradable nanoparticles would dissolve at a controlled rate designed to deliver appropriate doses of the drug to the brain over time. Another approach would be to deliver TRH powder by inhalation. This is the specific delivery system addressed in this communication, whereas opposed to intranasal delivery of nanoparticles.

Thyrotropin-releasing hormone has a euphoric, calming, antidepressant effect.[3] Thyrotropin-releasing hormone has been shown to decrease suicidal ideas, depression, and bipolar disorders. The release of norepinephrine in the brain induced by TRH may be the mechanism, whereby TRH reverses mental depression.[4]

Although some studies have confirmed the antidepressant efficacy of intravenously (IV) administered TRH, other studies did not confirm these findings.[3] However, administration of TRH by an intrathecal route induced a rapid improvement in mood and reduction in suicidality in patients with depression.

The mood improvement was short-lived, for example, 5 days in 1 subject.[3] In addition, the intrathecal route of administration would obviously be impractical.

Peptidases in the lung degrade some inhaled hormones.[5] However, experimental studies have shown that inhaled TRH should pass through the lung to the blood without significant peptidase degradation.[6,7] The fraction of inhaled TRH in the plasma after a single TRH inhalation at any time (t) can be calculated with the following formula[8]:

$$\frac{\lambda_1 \cdot (e^{-\lambda_1 \cdot t} - e^{-\lambda_2 \cdot t})}{\lambda_2 - \lambda_1},$$

where

$$\lambda_1 := \frac{\ln(2)}{60}$$

and

$$\lambda_2 := \frac{\ln(2)}{5.3}$$

The log P octanol/water of TRH is −2.26.[9] Small inhaled molecules with log P of less than zero have a half-life in the lung of approximately 60 minutes.[10] In a human study, the half-life of TRH in the blood is 5.3 minutes; the mean distribution volume of TRH is 15.7 L.[11] With these data, the plasma level of TRH versus time after a single inhalation can be calculated and plotted (Fig. 1).

A pharmacokinetic analysis is presented later. The inhaled TRH plasma data are analyzed with a 1-compartment model[12] in the same manner as plasma data after any extravascular input.

Because TRH is constantly diffusing from the lung to the blood, it does not quickly disappear from the plasma, as does parenteral TRH. The pharmacokinetic analysis indicates that the mean residence time of inhaled TRH in the blood after a single inhalation is 93 minutes, whereas opposed to 10.6 minutes after a single IV bolus.[11] The absolute inhaled TRH bioavailability is 0.47 or 47%.

The estimates of the percentage of circulating TRH (protirelin) that crosses the blood-brain barrier after IV administration range from 0.2% to 2.75%.[3] Taking the blood flow to the brain to be 800 mL/min,[13] extraction of TRH from the blood to be 1.38%, and TRH bioavailability (AUC 0-inf) of 4.834 min × μg/ml, then 53 μg of TRH will enter the brain after a single 10-mg TRH inhalation. A single intrathecal TRH dose of 500 μg is effective in relieving depression and suicidal thoughts.[3] Nine to 10 TRH inhalations would suffice to deliver this dose. With four 10 mg of TRH inhalations per hour, 500 μg of TRH could be delivered to the brain in approximately 2½ hours. However, smaller TRH doses might be effective, and fewer hours of inhalation might be sufficient.

Adverse effects after IV TRH administration are minimal. Nausea, flushing, urinary urgency, and mild rise in blood pressure have been reported. After intrathecal administration, shaking, sweating, shivering, restlessness, and mild rise in blood pressure were observed.[3]

This analysis of inhaled TRH pharmacokinetics suggests that further study of inhaled TRH for therapeutic purposes is warranted. It might be best to do the

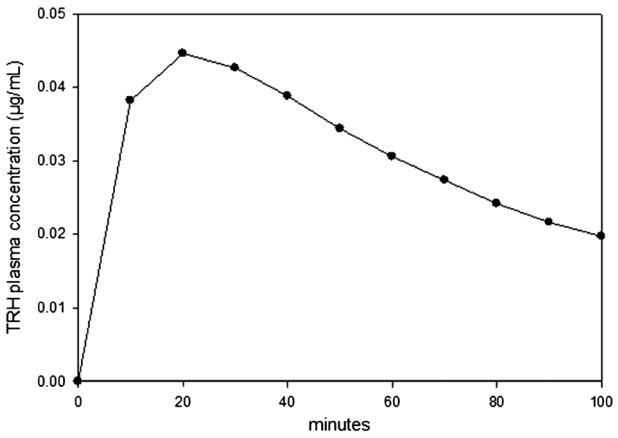

FIGURE 1. Predicted TRH plasma level after a single 10 mg inhalation.

analysis first in an animal model, or even an animal model of depression, to measure the amount of TRH in the brain.

The reanalysis of data presented previously was not part of the author's research group. Therefore, no institutional review board approval was indicated.

AUTHOR DISCLOSURE INFORMATION

Dr. Lehrer has filed a patent application for inhaled protirelin (TRH) as antidepressant.

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