NTP Update on
Vinpocetine: Prenatal Developmental Toxicity Study
May 2017

Synopsis
Vinpocetine is a dietary supplement that is asserted to enhance memory. The National Toxicology Program (NTP)\(^1\) evaluated the toxicity of vinpocetine in pregnant rats and rabbits.

A study with pregnant rats evaluated the effects of vinpocetine on maternal health and embryo and fetal development following oral administration at doses of 5, 20, and 60 mg/kg/day from gestation days 6 through 20. Increased embryo/fetal loss occurred in the 60-mg/kg/day dose group. Administration of vinpocetine also decreased fetal weight at all tested doses and induced fetal malformations in the two highest dose groups.

A study with pregnant rabbits evaluated the effects of vinpocetine on maternal health and embryo and fetal development (external evaluation only) following oral administration at doses of 25, 75, 150, and 300 mg/kg/day from gestation days 7 through 28. Decreased fetal weights were observed in the 75, 150, and 300-mg/kg/day dose groups, and embryo/fetal loss occurred in the 300-mg/kg/day dose group.

In summary, oral administration of vinpocetine to pregnant animals resulted in adverse effects on embryo and fetal development. The blood levels of vinpocetine measured in the pregnant animals were similar to those reported in the literature for humans after taking a single dose (10 mg) of vinpocetine.

Background
The prenatal developmental toxicity study in rats is used frequently to identify potential toxicity during embryo and fetal development. Pregnant rats are exposed to the chemical from gestation day 6 to gestation day 20, which covers the period following implantation of the rat embryo in the uterine lining to a developed rat fetus just before birth. During the exposure period, potential toxicity to the pregnant rat is assessed, and—following exposure—maternal health and fetuses are evaluated. This evaluation includes examining the fetus externally for potential adverse effects (changes in structure or appearance) on the internal organs and on the developing skeleton. Many fetuses (typically, 200–300 per dose group) are examined to detect subtle or rare changes, which might include malformations or indications of delayed growth as compared to unexposed fetuses.

\(^1\) NTP is a federal, interagency program that has as its goal to safeguard the public by identifying substances in the environment that might affect human health. NTP is headquartered at the National Institute of Environmental Health Sciences, which is part of the National Institutes of Health. For more information about NTP and its programs, visit \url{http://ntp.niehs.nih.gov/}. 
**Vinpocetine Study in Rats**

The doses for the comprehensive main study in rats were based on the findings in a preliminary study, where rats were administered vinpocetine at dose levels of 20, 40, 80, 160, and 320 mg/kg/day. In the subsequent, more comprehensive prenatal developmental toxicity study in which fetuses underwent detailed visceral and skeletal exams, vinpocetine was administered at dose levels of 0 (controls), 5, 20, and 60 mg/kg/day (in 0.5% methylcellulose vehicle) to pregnant Harlan Sprague Dawley rats via oral gavage from gestation day 6 to gestation day 20. Dams and fetuses were evaluated for several endpoints to identify any potential effects of vinpocetine.

At these dose levels, administration of vinpocetine to rats had no effect on maternal measurements, indicating that vinpocetine had selective effects on the fetuses. Exposure to vinpocetine, however, did result in clinical observations of brown and red vaginal discharge and decreased maternal body weights in the 60-mg/kg/day dose group, both of which were consistent with the 83% increase in post-implantation loss in this dose group. The increase in post-implantation loss in this dose group was due to an increase in resorptions early in pregnancy. Fetal weight adjusted for litter size was decreased significantly by 12% at 60 mg/kg/day, and a small decrease in fetal weight was observed in the 20-mg/kg/day dose group.

Specific malformations were increased in the 20- and 60-mg/kg/day dose groups. The malformations included increased incidences of ventricular septal (heart) defects and extra ribs in the thoracolumbar region of the fetus. Although not considered a malformation, increases in incomplete ossification (partially mineralized bone) of the thoracic centrum also were observed in fetuses in the 20- and 60-mg/kg/day dose groups. These effects on ossification are consistent with the decreased fetal weight, indicating delayed fetal growth.

**Vinpocetine Study in Rabbits**

A study in rabbits was conducted to determine if effects observed in the rat also were present in the rabbit, a commonly used nonrodent species for prenatal toxicity studies. Vinpocetine was administered at dose levels of 0 (controls), 25, 75, 150 and 300 mg/kg/day (in 0.5% methylcellulose vehicle) to pregnant New Zealand White rabbits via oral gavage from gestation day 7 to gestation day 28. Does and fetuses were evaluated for several endpoints (not including visceral and skeletal exams) to identify any potential effects of vinpocetine.

At these dose levels, administration of vinpocetine to rabbits resulted in no signs of maternal toxicity. Similar to what was seen in rats, clinical observations related to problems with pregnancy were observed in the 150- and 300-mg/kg/day dose groups. As a result of vinpocetine exposure, maternal body weight gain also decreased in the 150- and 300-mg/kg/day groups; however, the effect was not present when maternal body weight gain was adjusted for litter size. Post-implantation loss (20%, not statistically significant) slightly increased in the rabbits exposed to 300 mg/kg/day of vinpocetine, which resulted in fewer live fetuses. This result was attributable to the induction by vinpocetine of both early and late resorptions in the rabbits. Fetal weight adjusted for litter size was 16.5% lower in the 300-mg/kg/day dose group, and small decreases in fetal weight adjusted for litter size were observed in the 75- and 150-mg/kg/day dose groups.
Summary

Oral administration of vinpocetine to pregnant animals resulted in adverse effects on fetal development, including increased embryo/fetal loss and decreased fetal weights in both rats and rabbits, and an increase in structural malformations in fetal rats. Many factors determine whether toxicity in animal studies translate to similar effects in humans, such as the amount and duration of exposure, differences in how the human body handles the chemical compared to other species, and whether the biological basis for the effect is similar between different species and humans. To better understand the exposure across species, blood levels of vinpocetine were measured in the pregnant animals. The blood levels of vinpocetine were comparable to those reported in the literature for humans after taking a single dose (10 mg) of vinpocetine.

Next Steps

A comprehensive report of these studies is currently in progress. The draft report is anticipated to be released for external peer review and public comment in late summer 2017.