

Gene Variant May Be Key to Fentanyl Response

Patients with the genetic variant didn't require as much fentanyl as did the patients without the variant.

BY BETSY BATES
Los Angeles Bureau

PALM DESERT, CALIF. — Women with a common genetic variant on the μ -opioid receptor had a markedly reduced need for intrathecal fentanyl during labor, raising the strong possibility that genes influence analgesic response to the drug.

An international research team that was led by Ruth Landau, M.D., of the University Hospital of Geneva, announced their findings at the annual meeting of the Society for Obstetric Anesthesia and Perinatology.

Genetic polymorphism of the μ -opioid receptor is very common, found in roughly 10%-28% of the world's population.

When Dr. Landau and her associates genotyped the DNA of 113 nulliparous Swiss women at less than 35 weeks' gestation, the A118G variant was discovered in 32%.

Patients who went into spontaneous early labor and requested analgesia all re-

ceived a starting dose of 18 mcg of fentanyl with a testing interval between patients of 2 mcg.

After that point, their fentanyl dose was allocated in a blinded fashion according to an up-down allocation protocol until anesthesia success was reached, defined as a visual analog score of 1 or less for at least 60 minutes.

Failure was defined as a patient not reaching that degree of pain relief within 20 minutes, or analgesia wearing off before 60 minutes.

Anesthesiologists and parturients were blinded as to genotype and total fentanyl doses required for successful anesthesia success.

Among 37 patients who have thus far met the study criteria, adequate pain relief was obtained at a dosage of 16 mcg in patients with the genetic A118G variant and 26.8 mcg in patients with the more typical gene receptor.

The difference between the two patient groups was very highly significant.

"We have demonstrated a highly significant 1.68-fold potentiation of intrathecal fentanyl effect by μ -opioid receptor A118 polymorphism," said Dr. Landau, who is chief of the anesthesiology clinic at the university.

"We were very impressed. We were expecting—I guess hoping for—a difference, but we didn't think it would be this big," she said.

Results of the study are preliminary, and enrollment continues.

Nonetheless, a number of other intriguing findings have already begun to emerge.

In a separate analysis of 52 patients whose labor was induced, fentanyl was administered in small to high doses in a random fashion until successful anesthesia was achieved. In that group, three women with the genetic variant achieved success at less than 10 mcg of fentanyl, a strikingly low dose.

Another five patients from the original genotyped cohort had such rapid cervical dilation they could not be included in the medication analysis. Interestingly, four of the five had the genetic variant although they represented a much smaller

number of total patients in the cohort.

Dr. Landau posed a number of possible explanations for the differences between patients with and without the gene variant.

The intrathecal fentanyl may have an enhanced effect on individuals with the polymorphism: These patients may have altered pain perception, or their labor progress may be different from individuals without the genetic variant.

"We are continuing to investigate this [difference]," she said.

Since its cloning in 1993, the μ -opioid receptor polymorphism has been the subject of numerous studies by investigators curious about its potential link to opiate addiction and alcoholism, according to Dr. Landau.

In vitro studies have shown that the variant greatly increases the binding affinity and potency of β -endorphins, but not morphine, and that it may alter the toxicity profile of morphine 6 glucuronide response.

Carriers of the polymorphism have been shown to have an increased pain threshold when exposed to pressure pain, she said. ■

Genetic Psychiatric Disorders Cited in Children With FAE

BY LINDA LITTLE
Contributing Writer

GRAPEVINE, TEX. — The behavioral and cognitive defects in children with fetal alcohol effects may be partly due to genetic psychiatric disorders, researchers reported in a poster presentation at a meeting sponsored by the American College of Medical Genetics.

"Physicians need to ask about psychiatric and behavioral illnesses in families when diagnosing children with fetal alcohol effects [FAE]," said Helga V. Toriello, Ph.D., director of genetics services, Spectrum Health, Grand Rapids, Mich. "Acquiring a family history is important, because they suddenly may be dealing with genetic factors rather than alcohol."

While the diagnostic criteria for fetal alcohol syndrome are firm, the criteria for fetal alcohol effects are less clear and may overlap with other psychiatric and behavioral disorders, she said.

Researchers at Spectrum and DeVos Children's Hospital, also in Grand Rapids, found that 95% of children thought to have fetal alcohol effects also had psychiatric or behavioral disorders and that 89% had a first-degree relative with a psychiatric or behavioral disorder.

The study included 100 children aged 3-19 years who had been seen to determine whether they had fetal alcohol syndrome. None of the children fit the criteria for fetal alcohol syndrome and thus could be considered to have FAE.

But after conducting family histories, the researchers found a high rate of psychiatric and behavioral illnesses such as bipolar de-

pression and attention-deficit disorder, not only in the children but in first-degree relatives.

"This raises the question of how much of the behavioral problems are due to psychiatric illness or alcohol exposure," she asked. "A genetic condition might be contributing to the child's behavior."

Psychiatric and behavioral problems such as depression, anxiety, bipolar disorder, and attention-deficit hyperactivity disorder are known to be highly heritable.

Additionally, there appears to be a comorbidity of alcoholism and mental illness. For example, at least 20% of those with mood or anxiety disorders also have substance abuse disorder. And at least 20% of those with substance abuse problems also have mood or anxiety disorders.

The researchers found that children with bipolar depression had split verbal and performance IQ, executive dysfunction, and attention problems—all common features also reported in children exposed to alcohol.

Also, some individuals with psychiatric and behavioral illnesses have similar characteristics as those exposed to alcohol prenatally. For example, in bipolar depression, there is sexually inappropriate behavior, anger, hyperactivity, and learning disabilities, features also found in alcohol exposure.

Dr. Toriello said the researchers are not saying that alcohol does not have an effect, but it may not be the only reason for the child's behavior. "When we did a family history there was a high frequency of one or both parents having a mental illness or behavioral disorder. It might be that a genetic condition is contributing to the child's behavior rather than strictly alcohol exposure." ■

Investigational Test Screens for Abnormalities in Early Pregnancy

BY JANE SALODOF MACNEIL
Southwest Bureau

LOS ANGELES — Scientists have developed a noninvasive "genetic Pap" test to screen for Down syndrome and other chromosomal abnormalities early in pregnancy.

The test analyzes trophoblast cells shed by the fetus and scraped from the cervix, investigator Moshe D. Fejgin, M.D., reported in an oral presentation at the annual meeting of the Society for Gynecologic Investigation.

Researchers found fetal cells in about 87% of nearly 500 samples from two studies. The test identified two cases of trisomy 21 and one case each of Turner's syndrome and Klinefelter's syndrome in 110 pregnancies, according to Dr. Fejgin of the Meir Medical Center in Kfar Saba, Israel.

Gender predictions were correct in 92% of samples, he said, with accuracy ranging from 89% in samples from women planning to complete their pregnancies and 94% from a group that chose termination. Dr. Fejgin described the test as 100% accurate in determining male gender.

"When you are running 80%-90% accuracy, it can be used as a diagnostic," Dr. Fejgin said.

He and his coinvestigators concluded that the "genetic Pap" has the potential to replace other noninvasive screening techniques for Down syndrome.

Their announced goal is to find an alternative to invasive procedures such as amniocentesis and chorionic villi sampling, which can be risky as well as costly.

The concept is not entirely new. Scientists have long attempted to isolate fetal cells from maternal blood for this purpose without success, according to

Dr. Fejgin.

Fetal cells are shed into the cervix between 5 and 12 weeks of gestation, Dr. Fejgin said, describing the time frame as a window of opportunity for the "genetic Pap."

After the cells are obtained with a cytobrush, the screening process includes immunohistochemistry and fluorescence in situ hybridization (FISH) analysis for gender and

for chromosomal abnormalities. The investigators have formed a company to commercialize the test, Dr. Fejgin added during an interview.

He said they plan to start clinical trials in Europe and the United States and plan to submit the test to the Food and Drug Administration for approval. ■

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