

Found: Most Cost-Effective Down Syndrome Test

BY HEIDI SPLETE

FROM THE AMERICAN JOURNAL OF
OBSTETRICS & GYNECOLOGY

Contingent screening for prenatal Down syndrome was the most cost-effective stratagem, compared with other screening protocols, based on data from a computer simulation study of 110,948 pregnancies.

Several screening options are available in Canada and the United States, but data to help clinicians

choose among the tests are limited, wrote Dr. Jean Gekas of the Centre Hospitalier de l'Université Laval in Quebec City, and colleagues.

The researchers used a computer model to analyze a virtual population of 110,948 pregnant women based on the demographic, genetic, and Down syndrome (DS) phenotype characteristics of the local population in Quebec. The tests included were the combined test, triple test, quadruple test, integrated test, serum integrated test, sequential screening test, contingent screening test, and amniocentesis for women aged 35 years and older (Am. J. Obstet. Gynecol. 2011;204:175.e1-8).

"The contingent strategy seems to be the most cost effective and is associated with an attractive rate of procedure-related euploid miscarriages and unnecessary terminations," they wrote. "Moreover, this screening option provides a majority of women with reassurance early in gestation and may minimize costs by limiting retesting."

Overall, the contingent screening test showed a cost-effectiveness ratio of \$26,833 Canadian dollars per case of DS. The next most cost-effective test was the serum integrated screening test, but the incremental cost-effectiveness ratio (ICER) between the serum integrated screening and contingent screening tests was \$3,815 Canadian dollars for every DS birth detected.

The combined test, currently popular in the United States and Canada, had a slightly higher cost-effectiveness ratio of \$47,358 Canadian dollars than does the contingent test, but it allowed 91% of women to be reassured in the first trimester, they said.

Similar results on major outcomes including false positives, unnecessary terminations, and DS pregnancies were observed for contingent tests and several other screening tests. But the contingent screening test was associated with one of the lowest rates of procedure-related miscarriages (10). The contingent test also allowed 78% of patients to be reassured in the first trimester.

The combined test was associated with the highest rate of DS pregnancies in the first trimester (90%), and the highest rates of procedure-related euploid miscarriages (71) and unnecessary terminations (24). The combined test was the most expensive of the tests that followed screening strategies, most likely due to the requirement of a nuchal fold transparency test, and the high rate of false positives and subsequent unnecessary terminations associated with it, Dr. Gekas and associates said.

The computer model showed that the integrated test had the lowest rate of procedure-related miscarriages. However, widespread use of the integrated test would prevent women from being reassured in the first trimester, they noted.

The study was limited by the lack of prospective data and the potential inability to generalize the results across countries, they said. However, "it is unlikely that a large-scale prospective clinical trial comparing these eight screening approaches could rapidly be organized across North America."

VITALS

Major Finding: Overall, the contingent screening test showed a cost-effectiveness ratio of \$26,833 Canadian dollars per case of DS. The next most cost-effective test was the serum integrated screening test, but the incremental cost-effectiveness ratio (ICER) between the serum integrated screening and contingent screening tests was \$3,815 Canadian dollars for every DS birth detected.

Data Source: A cost-effective study of Down syndrome screening tests based on a computer model including 110,948 pregnancies.

Disclosures: The journal did not provide any disclosure information.

Brief Summary (For full Prescribing Information refer to package insert.)

INDICATIONS AND USAGE

OFIRMEV™ (acetaminophen) injection is indicated for

- the management of mild to moderate pain
- the management of moderate to severe pain with adjunctive opioid analgesics
- the reduction of fever.

CONTRAINDICATIONS

Acetaminophen is contraindicated:

- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- in patients with severe hepatic impairment or severe active liver disease.

WARNINGS AND PRECAUTIONS

Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. Do not exceed the maximum recommended daily dose of acetaminophen.

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance \leq 30 mL/min).

Allergy and Hypersensitivity

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatic Injury
- Allergy and Hypersensitivity

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Adult Population

A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence \geq 3% and at a greater frequency than placebo are listed in Table 1. The most common adverse events in adult patients treated with OFIRMEV (incidence \geq 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

Table 1. Treatment-Emergent Adverse Reactions Occurring \geq 3% in OFIRMEV and at a Greater Frequency than Placebo in Placebo-Controlled, Repeated Dose Studies

System Organ Class – Preferred Term	OFIRMEV (N=402) n (%)	PLACEBO (N=379) n (%)
Gastrointestinal Disorders		
Nausea	138 (34)	119 (31)
Vomiting	62 (15)	42 (11)
General Disorders and Administration Site Conditions		
Pyrexia*	22 (5)	52 (14)
Nervous System Disorders		
Headache	39 (10)	33 (9)
Psychiatric Disorders		
Insomnia	30 (7)	21 (5)

* Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders:

anemia

General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral

Investigations: aspartate aminotransferase increased, breath sounds abnormal

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: muscle spasms, trismus

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hypertension, hypotension

Pediatric population

A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 59.7% (n=212) who received 5 or more doses and 43.1% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence \geq 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=355) that occurred with an incidence of at least 1%.

Blood and lymphatic system disorders: anemia

Cardiac disorders: tachycardia

Gastrointestinal disorders: abdominal pain, diarrhea

General disorders and administration site conditions: injection site pain, edema peripheral, pyrexia

Investigations: hepatic enzyme increase

Metabolism and nutrition disorders: hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia

Musculoskeletal and connective tissue disorders: muscle spasm, pain in extremity

Nervous system disorders: headache

Psychiatric disorders: insomnia

Renal and urinary disorders: oliguria

Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypoxia, pleural effusion, stridor, wheezing

Skin and subcutaneous tissue disorders: periorbital edema, rash

Vascular disorders: hypertension, hypotension

DRUG INTERACTIONS

Effects of other Substances on Acetaminophen

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

Anticoagulants

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen, and it is not known whether OFIRMEV can cause fetal harm when administered to a pregnant woman. OFIRMEV should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

Labor and Delivery

There are no adequate and well-controlled studies with OFIRMEV during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

Nursing Mothers

While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 – 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. Caution should be exercised when OFIRMEV is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (\geq 32 weeks post menstrual age) to adolescents. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age.

Geriatric Use

Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Hepatic Impairment

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. A reduced total daily dose of acetaminophen may be warranted.

Patients with Renal Impairment

In cases of severe renal impairment (creatinine clearance \leq 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.

OVERDOSAGE

Signs and Symptoms

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

PHARMACOKINETICS

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

The maximum concentration (C_{max}) occurs at the end of the 15 minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the C_{max} following administration of OFIRMEV is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

The pharmacokinetic exposure of OFIRMEV observed in children and adolescents is similar to adults, but higher in neonates and infants. Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to < 2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older.

NONCLINICAL TOXICOLOGY

Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the *in vitro* mouse lymphoma assay and the *in vitro* chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of fertility

In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

OFIRMEV (acetaminophen) injection

Manufactured for:
Cadence Pharmaceuticals, Inc.
San Diego, CA 92130

Revised 11/2010

© 2010 Cadence Pharmaceuticals, Inc. All rights reserved.
OFIRMEV and CADENCE™ are trademarks of Cadence Pharmaceuticals, Inc.
U.S. PATENT NUMBERS: 6,028,222; 6,992,218
OFV10471110B5

OFIRMEV
(acetaminophen) injection