| Adverse Event | amlodipine | | Placebo | |
|---|---|---|---|---|
| | M=% (N=1218) | F=% (N=512) | M=% (N=914) | F=% (N=336) |
| Edema | 5.6 | 14.6 | 1.4 | 5.1 |
| Flushing | 1.5 | 4.5 | 0.3 | 0.9 |
| Palpitations | 1.4 | 3.3 | 0.9 | 0.9 |
| Somnolence | 1.3 | 1.6 | 0.8 | 0.3 |

The following events occurred in ≤1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,** myalgia. **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea,** epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leukopenia, purpura, thrombocytopenia. The following events occurred in ≤0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. Clinical Adverse Experiences: Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 3.

**Table 3. Adverse Events in Placebo-Controlled Studies (% of Patients)**

| Body System/ Adverse Event | Placebo N=270 | atorvastatin 10 mg N=863 | 20 mg N=36 | 40 mg N=79 | 80 mg N=94 |
|---|---|---|---|---|---|
| **BODY AS A WHOLE** | | | | | |
| Infection | 10.0 | 10.3 | 2.8 | 10.1 | 7.4 |
| Headache | 7.0 | 5.4 | 16.7 | 2.5 | 6.4 |
| Accidental Injury | 3.7 | 4.2 | 0.0 | 1.3 | 3.2 |
| Flu Syndrome | 1.9 | 2.2 | 0.0 | 2.5 | 3.2 |
| Abdominal Pain | 0.7 | 2.8 | 0.0 | 3.8 | 2.1 |
| Back Pain | 3.0 | 2.8 | 0.0 | 3.8 | 1.1 |
| Allergic Reaction | 2.6 | 0.9 | 2.8 | 1.3 | 0.0 |
| Asthenia | 1.9 | 2.2 | 0.0 | 3.8 | 0.0 |
| **DIGESTIVE SYSTEM** | | | | | |
| Constipation | 1.8 | 2.1 | 0.0 | 2.5 | 1.1 |
| Diarrhea | 1.5 | 2.7 | 0.0 | 3.8 | 5.3 |
| Dyspepsia | 4.1 | 2.3 | 2.8 | 1.3 | 2.1 |
| Flatulence | 3.3 | 2.1 | 2.8 | 1.3 | 1.1 |
| **RESPIRATORY SYSTEM** | | | | | |
| Sinusitis | 2.6 | 2.8 | 0.0 | 2.5 | 6.4 |
| Pharyngitis | 1.5 | 2.5 | 0.0 | 1.3 | 2.1 |
| **SKIN AND APPENDAGES** | | | | | |
| Rash | 0.7 | 3.9 | 2.8 | 3.8 | 1.1 |
| **MUSCULOSKELETAL SYSTEM** | | | | | |
| Arthralgia | 1.5 | 2.0 | 0.0 | 5.1 | 0.0 |
| Myalgia | 1.1 | 3.2 | 5.6 | 1.3 | 0.0 |

***Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT):*** In ASCOT involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up. The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients. **Body as a Whole:** *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. **Musculoskeletal System:** *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. ***Postintroduction Reports with Atorvastatin:*** Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. ***Pediatric Patients (ages 10-17 years):*** In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **PRECAUTIONS, Pediatric Use**).

**OVERDOSAGE:** There is no information on overdosage with CADUET in humans. **Information on Amlodipine:** Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. **Information on Atorvastatin:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

*Based on patient weight of 50 kg.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

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# Preconception Dieting Ups Preterm Delivery Risk

BY KATE JOHNSON
*Montreal Bureau*

TORONTO — Women who diet to lose weight before getting pregnant could be at increased risk of giving birth prematurely, according to Jim Johnstone of the department of physiology at the University of Toronto.

The findings, which Mr. Johnstone presented at the annual meeting of the Society for Gynecologic Investigation, come from a subset of the Southampton Women's Survey, in which 12,500 women who were aged 24-34 years were interviewed before they became pregnant, and then 3,000 were followed through their subsequent pregnancies.

**Compared with nondieters, dieters had decreased levels of the enzyme 11b HSD2, indicating increased fetal exposure to cortisol.**

In Mr. Johnstone's sample of 605 of these pregnant women, 23% had indicated before conception that they were dieting to lose weight.

However, the time interval between the survey interview and their subsequent pregnancy was not recorded.

The analysis revealed that women who became pregnant after a weight loss diet were significantly more likely to give birth prematurely, compared with women who did not diet (11% vs. 5%).

This finding was independent of maternal body mass index, smoking status, exercise, socioeconomic status, ethnicity, and infant gender.

In addition, a total of 50 placental samples selected randomly from the group at term showed that—compared with nondieters—dieters had decreased levels of the enzyme 11b hydroxysteroid dehydrogenase type 2 (11b HSD2), indicating increased fetal exposure to cortisol, as well as increased levels of cyclooxygenase-2 (COX-2), indicating an increased placental capacity to produce prostaglandins.

"These findings suggest that influences associated with dieting behavior can alter the timing of parturition," concluded Mr. Johnstone.

In addition to animal data that support the link between preconception undernutrition and preterm birth, Mr. Johnstone said that human data show a significant increase in the incidence of preterm delivery related to the 1944-1945 famine in the Netherlands. ■

# *Nitroglycerin Patch Improves Preterm Neonatal Outcomes*

BY KATE JOHNSON
*Montreal Bureau*

TORONTO — Transdermal nitroglycerin improved neonatal outcome but did not significantly delay delivery according to the results of the Canadian Preterm Labour Nitroglycerin Trial.

"Given that there is no standard of care [for the management of preterm labor] and that no tocolytic has been shown to improve outcome, this is potentially very exciting," said principal investigator Dr. Graeme N. Smith of Queen's University in Kingston, Ontario. His center and several others have already adopted this approach as standard, he said in an interview.

The study, which he presented at the annual meeting of the Society for Gynecologic Investigation, randomized 158 women between 24 and 32 weeks' gestation and in preterm labor either to placebo (81 patients) or a transdermal nitroglycerin, or glyceryl trinitrate (GTN), patch (77 ).

The primary outcome measured was a neonatal morbidity composite which included one or more of the following: chronic lung disease, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and perinatal mortality. The secondary outcome was the time to delivery.

Upon entry into the study and before randomization, all women received a 500-mL saline bolus (0.9%) to offset the potentially dehydrating effects of GTN. The GTN patch delivered a dose of 0.4 mg/hr and was replaced once after 24 hours.

In the 153 women left in the final analysis, neonatal outcome was significantly improved in those receiving the GTN patch, with a composite score of 3, compared with a score of 11 in the placebo group, for a relative risk of 0.29. This effect was limited to those who were at 28 weeks' gestation or less. There was one case of chronic lung disease in the GTN group, compared with seven in placebo; two cases of IVH in the GTN group, compared with one in placebo; and no cases of NEC, PVL, or perinatal mortality in the GTN group, compared with two, two, and three cases, respectively, in the placebo group.

Although there was no significant effect of GTN on time to delivery, the medication resulted in a nonsignificant 7-day prolongation of pregnancy, said Dr. Smith, suggesting that the effect might have reached significance with higher numbers.

GTN is a smooth muscle relaxant and thus might relax the smooth muscle of the uterus, he said. This effect was not observed, so he suggested the improvement in neonatal outcome might result from improved blood flow to the placenta or uterus. Side effects were seen more in the GTN group, with a relative risk of 1.41, headache being the most common. ■