

# Hypofibrinolysis Linked With Increased VT Risk

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ORLANDO — Hypofibrinolysis is a risk factor for venous thrombosis, particularly in women, younger individuals, and those who also have Factor V Leiden, Dr. Mirjam E. Meltzer reported at the annual meeting of the American Society of Hematology.

In a study of 2,420 patients with a first episode of pulmonary embolism or deep

vein thrombosis of the leg, and 2,943 controls, increased clot lysis time (CLT) was associated with increased venous thrombosis risk, said Dr. Meltzer of University Medical Center, Utrecht, the Netherlands.

Lysis of a tissue factor–induced clot by exogenous tissue-type plasminogen activator was assessed by monitoring changes in turbidity during clot formation and subsequent lysis. Quartiles of CLT were established based on values in control subjects.

Each increasing quartile of CLT was

shown to be associated with an increase in venous thrombosis risk, she explained.

Individuals with hypofibrinolysis (those in the fourth quartile of CLT), compared with those in the first quartile, had an odds ratio for venous thrombosis of 1.8 after adjusting for age and sex. The risk was slightly higher in women and younger patients.

Women younger than 49 years had an odds ratio for venous thrombosis of 2.5, and those over age 49 years had an odds ratio of 1.7, compared with the 1.8 over-

all odds ratio. Women had an overall odds ratio of 2.7, compared with 1.6 for men.

Participants were aged 18-70 years, and were from the Multiple Environmental and Genetic Assessment (MEGA) of risk factors for venous thrombosis study, a population-based, case-control study.

Venous thrombosis risk in this analysis was determined for hypofibrinolysis alone, and in combination with Factor V Leiden and prothrombin 20210A mutations. Risk was increased threefold in those with Factor V Leiden alone, and sevenfold in those with both hypofibrinolysis and Factor V Leiden, compared with subjects in the first quartile of CLT, Dr. Meltzer said.

A similar analysis of those with hypofibrinolysis and the prothrombin 20210A mutation showed the mutation did not enhance the risk over the threefold increased risk in those with prothrombin 20210A alone.

The findings confirm those from smaller studies showing a link between hypofibrinolysis and increased venous thrombosis risk, she noted. ■

## HDL May Protect Against Venous Thrombosis

ORLANDO — High-density lipoproteins, which are known protectors against arterial atherothrombosis, also appear to protect against recurrent venous thrombosis, Dr. Sabine Eichinger reported at the annual meeting of the American Society of Hematology.

In a prospective study of 772 patients with a first episode of spontaneous venous thromboembolism, the relationship between plasma lipoprotein parameters and recurrence of venous thrombosis was evaluated. Of the 772 patients, 100 (13%) had recurrent VTE during an average follow-up of 4 years.

Compared with patients without recurrence, those with recurrence had significantly lower mean plasma levels of apolipoprotein A-I, a major component of HDL (1.12 vs. 1.23 mg/mL), said Dr. Eichinger of the Medical University of Vienna.

The relative risk of recurrence in this study population was 0.87 for each increase of 0.1 mg/mL in plasma apolipoprotein A-I; for those with apolipoprotein A-I levels above the 67th percentile, compared with those with lower levels, relative risk of recurrence was 0.51.

Further, HDL cholesterol levels and HDL particle concentrations were lower in patients with recurrence, she noted.

Although it was thought that HDL is protective against recurrent venous thrombosis as a result of its multiple antithrombotic and anti-inflammatory actions, this had not been previously shown, she explained.

Measurement of HDL parameters may be useful for predicting venous thrombosis recurrence risk, and drugs that increase HDL might be useful for reducing venous thrombotic events, she concluded.

—Sharon Worcester

### Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed ADACEL™

**Brief Summary:** Please see package insert for full prescribing information

**INDICATIONS AND USAGE** ADACEL vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of ADACEL vaccine as a primary series, or to complete the primary series, has not been studied. As with any vaccine, ADACEL vaccine may not protect 100% of vaccinated individuals.

**CONTRAINDICATIONS** Known systemic hypersensitivity to any component of ADACEL vaccine or a life-threatening reaction after previous administration of the vaccine or a vaccine containing the same substances are contraindications to vaccination with ADACEL vaccine. Because of uncertainty as to which component of the vaccine may be responsible, additional vaccinations with the diphtheria, tetanus or pertussis components should not be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. The following events are contraindications to administration of any pertussis containing vaccine: (1) Encephalopathy within 7 days of a previous dose of pertussis containing vaccine not attributable to another identifiable cause. (2) Progressive neurological disorder, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established, the condition has stabilized, and the benefit clearly outweighs the risk. (3) ADACEL vaccine is not contraindicated for use in individuals with HIV infection. (4) **WARNINGS** Because intramuscular injection can cause injection site hematoma, ADACEL vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer ADACEL vaccine in such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection. (1) If any of the following events occurred in temporal relation to previous receipt of a vaccine containing a whole-cell pertussis (eg, DTP) or an acellular pertussis component, the decision to give ADACEL vaccine should be based on careful consideration of the potential benefits and possible risks: (2) (3) • Temperature of 104.0°F (40.0°C) within 48 hours not due to another identifiable cause; • Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours; • Persistent, inconsolable crying lasting 3 hours, occurring within 48 hours; • Seizures with or without fever occurring within 3 days. When a decision is made to withhold pertussis vaccine, Td vaccine should be given. Persons who experienced Arthus-type hypersensitivity reactions (eg, severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid-containing vaccines more frequently than every 10 years, even if the wound is neither clean nor minor. (4) (5) If Guillain-Barré Syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give ADACEL vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (1) The decision to administer a pertussis-containing vaccine to individuals with stable central nervous system (CNS) disorders must be made by the health-care provider on an individual basis, with consideration of all relevant factors and assessment of potential risks and benefits for that individual. The ACIP has issued guidelines for immunizing such individuals. (2) A family history of seizures or other CNS disorders is not a contraindication to pertussis vaccine. (2) The ACIP has published guidelines for vaccination of persons with recent or acute illness. (1) **PRECAUTIONS** **General** Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel. ADACEL vaccine should not be administered into the buttocks nor by the intradermal route, since these methods of administration have not been studied; a weaker immune response has been observed when these routes of administration have been used with other vaccines. (1) The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case of an anaphylactic or acute hypersensitivity reaction occurs. Prior to administration of ADACEL vaccine, the vaccine recipient and/or the parent or guardian must be asked about personal health history, including immunization history, current health status and any adverse event after previous immunizations. In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of ADACEL vaccine must be carefully considered. The ACIP has published guidelines for the immunization of immunocompromised individuals. (6) Immune responses to inactivated vaccines and toxoids when given to immunocompromised persons may be suboptimal. (1) The immune response to ADACEL vaccine administered to immunocompromised persons (whether from disease or treatment) has not been studied. A separate, sterile syringe and needle, or a sterile disposable unit, must be used for each person to prevent transmission of blood borne infectious agents. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

**Information for Vaccine Recipients and/or Parent or Guardian** Before administration of ADACEL vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with ADACEL vaccine or other vaccines containing similar components. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of childbearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ADACEL vaccine. If they are pregnant or become aware they were pregnant at the time of ADACEL vaccine immunization, they should contact their health-care professional or Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). The health-care provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. (7) The toll-free number for VAERS forms and information is 1-800-822-7967 or visit the VAERS website at <http://www.fda.gov/oc/ir/ra/raers/raers.htm>

**Drug Interactions** Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See PRECAUTIONS, General.) For information regarding simultaneous administration with other vaccines refer to the ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** No studies have been performed with ADACEL vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

**Pregnancy Category C** Animal reproduction studies have not been conducted with ADACEL vaccine. It is also not known whether ADACEL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ADACEL vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with ADACEL vaccine. The effect of ADACEL vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered ADACEL vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of ADACEL vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study. (8)

**Pregnancy Registry** Health-care providers are encouraged to register pregnant women who receive ADACEL vaccine in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463 (1-800-VACCINE).

**Nursing Mothers** It is not known whether ADACEL vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ADACEL vaccine is given to a nursing woman.

**Pediatric Use** ADACEL vaccine is not indicated for individuals less than 11 years of age. (See INDICATIONS AND USAGE.) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis refer to manufacturers' package inserts for DTPa vaccines.

**Geriatric Use** ADACEL vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of ADACEL vaccine in individuals 65 years of age and older as clinical studies of ADACEL vaccine did not include subjects in the geriatric population.

**ADVERSE REACTIONS** The safety of ADACEL vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single booster dose of ADACEL vaccine. The principal safety study was a randomized, observer blind, active controlled trial that enrolled participants 11-17 years of age (ADACEL vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (ADACEL vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Observer blind design, ie, study personnel collecting the safety data differed from personnel administering the vaccines, was used due to different vaccine packaging (ADA-

CEL vaccine supplied in single dose vials; Td vaccine supplied in multi-dose vials). Solicited local and systemic reactions and unsolicited events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician's office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained via a scripted telephone interview. Approximately 96% of participants completed the 6-month follow-up evaluation. In the concomitant vaccination study with ADACEL and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Local adverse events were only monitored at site/arm of ADACEL vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, ie, up to six months post-vaccination. In the concomitant vaccination study with ADACEL vaccine and trivalent inactivated influenza vaccines local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, ie, up to 84 days, only events that elicited seeking medical attention were collected. In all studies, subjects were monitored for serious adverse events throughout the duration of the study. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

**Serious Adverse Events in All Safety Studies** Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of ADACEL vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neuropathic events that occurred within 28 days of ADACEL vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neuropathic events reported.

**Solicited Adverse Events in the Principal Safety Study** The frequency of selected solicited adverse events (erythema, swelling, pain and fever) occurring during Days 0-14 following one dose of ADACEL vaccine or Td vaccine were reported at a similar frequency in both groups. Few participants (<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 62-78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of ADACEL vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the two groups. Rates of pain did not significantly differ for adults. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in ADACEL vaccine recipients than Td vaccine recipients. (8) The rates of other local and systemic solicited reactions occurred at similar rates in ADACEL vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). Headache was the most frequent systemic reaction and was usually of mild to moderate intensity.

**Adverse Events in the Concomitant Vaccine Studies**

**Local and Systemic Reactions when Given with Hepatitis B Vaccine** The rates reported for fever and injection site pain (at the ADACEL vaccine administration site) were similar when ADACEL and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the ADACEL vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (8)

**Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine** The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of ADACEL vaccine and Td. However, pain at the ADACEL vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (8)

**Additional Studies** An additional 1,806 adolescents received ADACEL vaccine as part of the lot consistency study used to support ADACEL vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of ADACEL vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all subjects. Headache was the most frequently reported systemic event occurring in approximately 44% of all subjects. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (8) An additional 962 adolescents and adults received ADACEL vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following ADACEL vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing 'any' local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in the four principal trials. (8) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 ADACEL vaccine recipients.

**Postmarketing Reports** The following adverse events have been spontaneously reported during the post-marketing use of ADACEL vaccine in other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to ADACEL vaccine. General disorders and administration site conditions: injection site bruising, sterile abscess; skin and subcutaneous tissue disorders: pruritus, urticaria. There have been spontaneous reports of nervous system disorders such as myelitis, syncope vasovagal, paresthesia, hypoesthesia and musculoskeletal and connective tissue disorders such as myositis and muscle spasms temporally associated with ADACEL vaccine.

**Reporting of Adverse Events** The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this ADACEL vaccine package insert. (7) (9) (10) The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at <http://www.fda.gov/oc/ir/ra/raers/raers.htm>. (7) (9) (10) Health-care providers should also report these events to Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

**DOSAGE AND ADMINISTRATION** ADACEL vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route. SHAKE THE VIAL WELL to distribute the suspension uniformly before withdrawing the 0.5 mL dose for administration. Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine. Do NOT administer this product intravenously or subcutaneously.

**STORAGE** Store at 2° to 8°C (35° - 46°F). DO NOT FREEZE. Discard product if exposed to freezing. Do not use after expiration date.

**REFERENCES** 1. CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR-2):1-35. 2. CDC. Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children. Recommendations of the ACIP. MMWR 1997;46(RR-7):1-25. 3. CDC Update. Vaccine side effects, adverse reactions, contraindications and precautions - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(RR-12):1-35. 4. CDC. Update on adult immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1991;40(RR-12):1-52. 5. CDC. Diphtheria, tetanus and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-10):1-28. 6. CDC. Use of vaccines and immune globulins in persons with altered immunocompetence. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1993;42(RR-4):1-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(41):730-3. 8. Data on file at Sanofi Pasteur Limited. 9. CDC. Current trends - national vaccine injury act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37(13):197-200. 10. FDA. New reporting requirements for vaccine adverse events. FDA Drug Bull 1988;18(2):16-8.

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