The risk of adverse reactions from percutaneous prick-puncture allergen skin testing, venipuncture, and body measurements: Data from the second National Health and Nutrition Examination Survey 1976-80 (NHANES II)

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A sample (N = 16,204) of the U.S. population, 6 to 74 years of age, was examined in NHANES II with a variety of routine medical procedures, including prick-puncture allergen skin testing (AST), venipuncture, and body measurements. Eight unstandardized extracts licensed by the Food and Drug Administration, a positive and negative control, were used. AST was performed to screen the population for immediate hypersensitivity responses to common aeroallergens. No anaphylactic reactions after AST were observed. One asthmatic reaction occurred during venipuncture. Other adverse reactions (ARs) were limited to syncope, near syncope, and malaise. The rates for any AR were venipuncture, 0.49% (95% confidence interval [CI], 0.38% to 0.60%); AST, 0.04% (95% CI, 0.01%-0.08%); body measures, 0.006% (95% CI, 0 to 0.018%). Sex or fasting status had little effect on the occurrence of AR. The age group 20 to 49 years had the highest occurrence of any AR to venipuncture (0.87%; 95% CI, 0.633% to 1.107%). The risk of prick-puncture AST with eight extracts licensed by the Food and Drug Administration is low and similar to other routine medical procedures. (J ALLERGY CLIN IMMUNOL 1989;84:886-90.)

It is important for physicians and health care workers performing routine diagnostic medical procedures to have a reliable estimate of the hazards associated with these procedures. This knowledge will facilitate patient acceptance of these procedures by allaying unnecessary fears. No estimates of the rate of ARs associated with the routine diagnostic procedure, venipuncture, were found in a review of current medical textbooks.[1-4] Similarly, recent textbooks of allergy have either not reported rates of adverse effects from prick-puncture AST[5] or cited the experience from a single foreign clinic.[6]

Abbreviations used

AST:	Allergen skin testing
AR:	Adverse reaction
NHANES:	National Health and Nutrition Examination Survey
FDA:	Food and Drug Administration
CI:	Confidence interval
NCHS:	National Center for Health Statistics

The second NHANES, 1976-1980, conducted by the NCHS, was based on a sample of the U.S. population.[7] During NHANES II, examinees underwent a variety of routine diagnostic procedures, including percutaneous prick-puncture AST, venipuncture, and body measurements. In addition to collecting the re-

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sults of these diagnostic procedures, the staff maintained a record of ARs associated with these procedures. Because AST was performed, concern regarding anaphylaxis prompted a review of the records for adverse results compatible with systemic adverse allergic responses. This review afforded an opportunity to assess the risk associated with these routinely administered diagnostic procedures in a general population sample.

METHODS

Survey

The NHANES II was a national sample of the civilian, noninstitutional population of the United States conducted at 64 sampling sites during 1976 to 1980. It was based on a stratified multistage, probability cluster sample of households. When the appropriate sampling weights are used, the estimates from the sample represent the U.S. population on March 1, 1978.[7]

Both interview and examination procedures were used to collect a broad spectrum of health data on participants in NHANES II. To ensure that all procedures were conducted in a standardized environment throughout the survey, the interviewers, technicians, and mobile examination centers were moved to each of the 64 examination sites. Details of the NHANES II design, sample selection, operational plan, and quality control have been published previously.[7]

Study population

All examined sample subjects 6 to 74 years of age were scheduled to receive body measurements, venipuncture, and percutaneous prick-puncture AST, in addition to other tests. A half sample of 20 to 74-year-old subjects were required to fast before coming into the examination center. All tests were performed on the same day in random order on each sample subject.

Test procedures

Venipuncture. Blood was drawn with either a vacutainer or a butterfly from the antecubital fossa with 20- to 22-gauge needles.[8] Amounts withdrawn were age linked: 6 to 11 years, 50 ml; 12 to 19 years, 65 ml; and 20 to 74 years, 80 ml. Participation rate was 97.7%.

AST procedures. Eight unstandardized allergenic extracts, licensed by the FDA (1:20 wt/vol, 50% glycerol, vol/vol), of short/giant ragweed, oak, *Alternaria*, ryegrass, Bermuda grass, cat, dog, and house dust, plus a positive control (FDA-approved histamine base) and a negative control (50% glycerol, vol/vol), were administered. This battery of allergens was selected to be representative of important aeroallergens from a variety of sources. The battery was used to elicit immediate hypersensitivity responses in the general U.S. population, regardless of region. The battery was not intended to serve as a diagnostic evaluation of the allergic status of any individual tested.

The allergens were applied to the volar surface of the arm by the prick-puncture (Pepys) method with 25-gauge BD needles.[9] The prick-puncture method entails simultaneous piercing of the extract drop and the superficial skin layers with the tip of the needle. The needle tip is then lifted to tent the skin in order to create a needle track into which extract flows.

The participation rate was 97.5%. The 410 sample subjects not tested had a higher prevalence of asthma and/or hay fever than the tested population (55% versus 12%).

Body measurements. Height, weight, body circumferences, and skin folds were obtained in both sitting and standing positions. Participation rate was 99%.

ARs

The occurrence of ARs was based on observations made by the technicians during the examination, not by routine questioning of the sample subjects, and occurrences were recorded in an AR logbook. These ARs were categorized by the authors as allergic reactions: anaphylaxis, asthma; or nonallergic reactions: syncope, when unconsciousness was reported; nearsyncope, when light-headedness was reported; or malaise, if other systemic symptoms were reported.

Statistical methods

Since the purpose of this study was not to make national estimates but rather to report on the experiences of a large survey, the weights and complex survey design were not used. All estimates reported are unweighted, and the variances are based on the simple random-sample assumption.

RESULTS

A tabulation of the number of adverse reactions, both allergic and nonallergic, for each medical test procedure is presented in Table I. Most ARs occurred during the venipuncture. The only "allergic-type" reaction occurred during venipuncture. This asthmatic reaction was observed in an 8-year-old black male child who experienced the attack while he was crying because of the venipuncture.

The observed rates of any AR for each medical procedure are presented in Table II. Venipuncture had the highest rate of reactions (0.49%) (95% CI, 0.38% to 0.60%), and body measures the lowest rate (0.006%) (95% CI, 0 to 0.018%). AST reaction rate was intermediate (0.04%) (95% CI, 0.01% to 0.08%).

The percent with any AR by sex, fasting status, race, and age are presented in Table III. The age group 20 to 49 years had the highest occurrence of reactions to venipuncture with the 6- to 19-years and 50- to 74-years age groups having approximately equivalent rates. White subjects had a higher rate of ARs to venipuncture than did black subjects, but the difference was not statistically significant. A half sample of 20- to 74-year-old subjects were required to fast

TABLE I. Number of ARs by procedure in examinees 6 to 74 years of age

	Procedure		
	AST (N = 15,794)	Venipuncture (N = 15,858)	Body measurements (N = 16,204)
Allergic reactions			
Total	0	1	0
Asthma	0	1	0
Anaphylaxis	0	0	0
Nonallergic reactions			
Total	7	77	1
Syncope	6	26	1
Near syncope	0	39	0
Malaise	1	12	0

Source: NHANES II, 1976-80, conducted by NCHS.

TABLE II. Percent with any AR by procedure for examinees 6 to 74 years of age

Procedure	%	95% CI
Venipuncture	0.49	0.38-0.60
AST	0.04	0.01-0.08
Body measurements	0.006	0.0-0.018

Source: NHANES II, 1976-80, conducted by NCHS.

before the examination. The sex or fasting status of an individual had little effect on the occurrence of AR outcomes during AST or venipuncture.

DISCUSSION

The estimated risks of ARs for the procedures in NHANES II probably underestimate the actual risks for these procedures for a number of reasons. It is likely that some ARs were not recorded by the technicians in the log-books. It is unlikely, however, that this underreporting occurred more often in any one procedure. The results for AST only apply to prick-puncture testing with eight allergens. The risks from more invasive skin test procedures or use of more than eight allergens are likely to be higher than that observed in NHANES II. The estimates are based on a medically low-risk population and therefore are likely to underestimate the prevalence of ARs in a medically high-risk population. And finally, because of the extremely low occurrence of these risks, the sample size (approximately 16,000) may not have been sufficient to detect a very rare occurrence, for example, an "allergic response" caused by AST.

The ordering of the rates of ARs is concordant with the phobia literature in which the rates of syncope are dependent on the perceived intensity of injury or blood eliciting properties for the procedure.[10] The highest rate occurred in the most invasive blood-associated procedure (venipuncture), whereas the lowest rate occurred in a noninvasive nonblood associated procedure (body measurements). Prick-puncture AST, a minimally invasive, nonblood-eliciting procedure, was intermediate.

The age peak (20 to 49 years) observed for ARs caused by venipuncture also follows the age distribution of phobias. The age peak for seeking medical treatment for blood/injury/illness phobias is 28 to 32 years.[10] In addition, although 3% to 4% of the total population is phobic to either blood or injury,[11] a much higher percent, 14.5%, of a college-aged sample has reported either fainting or near fainting in response to the sight of blood or injury.[12] These data suggest that many of the ARs observed in NHANES II may be the result of phobia responses to blood or injury.

In comparing the rates of ARs observed in NHANES II to other similar procedures, two points should be considered, (1) the blood, injury, or illness eliciting properties of the procedures and (2) the medical characteristics of the populations.

The only source of data for comparison to the ARs observed caused by venipuncture is from blood donations, a more invasive, blood-eliciting procedure. The rate of syncope during blood donation has been reported to be 4% of donors,[13] a rate substantially higher than that observed for venipuncture in this study. Two fatalities after blood dontion have been

TABLE III. Percentage of any AR by sex in examinees 6 to 74 years of age

	Sample size	%	95% CI
Venipuncture			
Age (yr)			
6-19	4121	0.34	0.162-0.518
20-49	5880	0.87	0.633-1.107
50-74	5857	0.22	0.100-0.340
Sex			
M	7690	0.53	0.367-0.693
F	8168	0.45	0.305-0.595
Race			
White	13902	0.53	0.410-0.650
Black	1956	0.26	0.037-0.483
Fasting status*			
Fasting	5822	0.46	0.286-0.634
Nonfasting	5915	0.63	0.428-0.832
AST			
Sex			
M	7654	0.05	0.000-0.101
F	8140	0.04	0.000-0.081
Fasting status*			
Fasting	5759	0.02	0.000-0.053
Nonfasting	5832	0.02	0.000-0.053

Source: NHANES II, 1976-80, conducted by NCHS.
*A half sample of 20- to 74-year-old subjects were required to fast before coming into the examination center.

reported between 1976 and 1985 (Sazama K. Personal communication. Division of Blood and Blood Products, FDA). Consistent with the higher rate of syncope observed in white subjects after venipuncture in NHANES II, a significantly much higher rate of syncope in white subjects has been reported after blood donation.[10]

The risk of prick-puncture AST in NHANES II in which 12% of the population had histories of either allergic rhinitis or asthma and 20.2% reacted with a positive skin test to at least one allergen[9] can be compared to published results of intradermal allergy testing, a more invasive procedure. AR rates of 1%[14] and 2%[15] have been reported after intradermal injection of penicillin and Hymenoptera venom during diagnostic testing of patients with histories of suspected anaphylaxis caused by penicillin and bee sting, respectively. These rates are likely to be higher than that attributable to the intradermal injection itself due to the higher rates of skin test positivity in these populations, exposure to larger quantities of allergen, and the emotionally charged medical context. In contrast to intradermal testing, no fatalities from prick-puncture AST have been reported in the past two decades.[16]

With these caveats in mind, the AR rates observed in NHANES II can be considered conservative estimates against which the risks in medically indicated high-risk populations can be compared. Heightened awareness by medical and health personnel of the prevalence of blood, injury, and illness phobias in the population should serve to encourage recognition of such patients, resulting in attempts at therapeutic interventions to reduce their risk.

Based on the results of NHANES II, prick-puncture AST with eight FDA-approved extract concentrates can be considered a low-risk medical procedure. Regardless of the perceived safety of the test procedure, it is prudent for trained nonmedical personnel performing these low-risk procedures to do so in a context where there is access to an individual certified in cardiopulmonary resuscitation. Additionally, for AST in which there is a remote possibility of anaphylaxis, there should be immediate access to a physician or a nurse, functioning under the guidance of a physician, who can administer epinephrine.

The third NHANES (1988 to 1994) will provide confirmatory data of the reproducibility of the AR estimates obtained in NHANES II.

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