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Electrocardiography Screening for Cardiotoxicity after Modified Vaccinia Ankara Vaccination

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Abstract

Background—Recently, symptomatic myopericarditis has been described following smallpox vaccination using replication-competent vaccinia strains.

Methods—We examined the incidence of new electrocardiogram (ECG) abnormalities and evaluated the safety and immunogenicity related to vaccination. Volunteer subjects (n=90) aged 18–32 years were enrolled in a National Institutes of Health (NIH) sponsored phase I smallpox vaccination trial (DMID 02-017) and observed over a 26-week period following 2 injections of IMVAMUNE®, Modified Vaccinia Ankara vaccine, (Bavarian Nordic A/S, Copenhagen, DK) followed by scarification with Dryvax®. Diagnostic computer-derived ECG statements were available to the clinical study team and compared to those of a board certified cardiologist who independently read the ECG tracings.

Results—Serial ECG tracings available for 89 of the subjects revealed new ST segment abnormalities in 2.2% and new T wave abnormalities in 15.7%; the majority (71.4%) resolved on subsequent tracings. Cardiologist over-read of computer statements resulted in frequent changes in readings, particularly negation of cardiac arrhythmias. A cardiology consultation was requested in 17 subjects for nonspecific cardiac symptoms or new abnormal ECG findings. Echocardiograms were performed in 12 of the 17 subjects and were normal except for 1 subject with possible myopericarditis after receiving Dryvax®.

Conclusions—New minor ECG abnormalities are common in apparently young healthy volunteers considered for smallpox vaccination trials. Cardiologist over-read of computer generated ECG statements in vaccine trials using ECG as a screening tool for safety can reduce false positive computer determined ECG diagnoses and reduce the need for inappropriate cardiology referral and additional non-invasive testing.

Keywords

Electrocardiography; smallpox vaccine; Modified Vaccinia Ankara (MVA); early repolarization; myopericarditis

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INTRODUCTION

Large scale smallpox vaccination programs were initiated by the US Department of Defense (DoD) in 2002 to vaccinate healthy military personnel and by the US Department of Health and Human Services (DHHS) in 2003 to vaccinate early responders in preparation for a potential bioterrorism attack involving the use of smallpox. Cardiac complications, consisting primarily of myopericarditis, and rarely acute coronary syndrome or death, have been reported within 30 days post-vaccination in these programs. Vaccinated subjects received the New York City Board of Health (NYCBOH) vaccinia strain (Dryvax®).[1] To more clearly identify subjects with a potential subclinical as well as symptomatic cardiac complication (e.g. myocardial ischemia, myocarditis, or pericarditis), due to potential cardiotoxicity, early phase vaccinia trials attempt to screen out subjects at high risk for cardiac events by requiring baseline and follow-up electrocardiograms (ECG) and active solicitation of symptoms to screen for abnormalities that might indicate that the volunteer is at risk for developing cardiac complications after vaccination. ECG manifestations of myopericarditis include cardiac arrhythmias, conduction disturbances, and repolarization abnormalities.[1,2] In healthy young adults, the ECG diagnosis can be confounded by early repolarization.[3]

In this report, we examine the incidence rates of new electrocardiographic abnormalities in subjects enrolled in a National Institutes of Health (NIH) sponsored phase I smallpox vaccine trial (DMID 02-017)[4] developed to provide protection to the populations at risk for complications with the present day replication-competent vaccines, with Dryvax®, a licensed replicating vaccine.

METHODS

Subject Selection

Two hundred and twelve healthy adults ages 18–32 years were screened for eligibility to participate in a NIH sponsored phase 1 clinical trial (DMID 02-017)[4] of 2 injections of IMVAMUNE® (Bavarian Nordic A/S, Kvistgard, Denmark) followed by scarification with Dryvax® (Wyeth Laboratories, Marietta, PA) between May 10, 2004 and June 9, 2005 (Table 1). Volunteers were ineligible if they had a prior smallpox vaccination, tested positive for human immunodeficiency virus (HIV) or hepatitis, had a prior history of active cardiovascular disease, or had major ECG abnormalities at screening.. The protocol was approved by the Saint Louis University Human Research Committee and all subjects provided written informed consent. Of the 212 subjects who were screened, 90 (42.5%) met all eligibility criteria.

The enrolled subjects were assigned to receive 2 injections of the same IMVAMUNE® dose [1×10^8, 2×10^7 or 1×10^5 tissue culture infective dose 50 ($TCID_{50}$)] or saline placebo followed by a standard dose [1×10^8 plaque forming units (pfu)] of Dryvax® or placebo after randomization on Day 0, Week 4 and Week 16 (Table 1)[4]. For purposes of ECG analysis Group 1 (n=60) is comprised of 4 study arms that received IMVAMUNE®, IMVAMUNE®, Dryvax®; Group 2 (n=15) received Placebo, Placebo, Dryvax®; and Group 3 (n=15) received IMVAMUNE®, IMVAMUNE®, Placebo.

The protocol required a resting 12 lead ECG at baseline, and at post-randomization visit weeks 2, 4, 6, 8, 16, 18, 20 and 26 as one of the methods used to screen for potential myocardial toxicity (myocardial ischemia, myocarditis or pericarditis), as well as cardiac troponin I measurements at baseline and at 2, 6 and 18 weeks post-vaccination. Subjects with suspect cardiac findings during follow-up were referred to a board certified cardiologist for additional workup that included supplemental ECG, cardiac troponin measurements and when indicated,

an echocardiogram. Of the 90 subjects, 1 dropped out after the initial vaccination prior to a follow-up ECG leaving 89 subjects available for post-randomization ECG analysis.

ECG Analysis

All ECG were acquired on a MAC 1200 electrocardiograph (GE Medical Systems) and transmitted to a dedicated MUSE analysis ECG system (Version 005E.08) for analysis and storage. Interval measurements were performed by an experienced research technician using the GE on-screen high-resolution caliper program. Morphologic assessment of the ECG tracing was performed by the cardiologist using an adaptation of the Minnesota code.[4] Interpretative statements of the MUSE 12SL program were available to the clinical unit at the time of the ECG recording. Diagnostic statements by the computer were compared to the final interpretation by the board certified cardiologist. Early repolarization was defined as J-point and ST segment elevation, had to occur in at least 2 consecutive beats and measure ≥ 0.2mV in leads V1 or V3, or ≥ 0.3mV in V2, or ≥ 0.1mV in the remaining leads with upward concavity of the ST segment. A notch or slur on the terminal portion of the QRS complex was required if present in leads V1–V3. The PR segment was compared to the TP segment in the initial evaluation of the ECG. The PQ junction was used to determine J-point and ST segment offsets in the absence of important PR depression.[5,6] Serial tracings were compared to baseline and the preceding tracing to determine morphological changes blinded to treatment assignment.

Computer determined GE 12SL diagnostic statements printed on the 12-lead ECG output were recorded. The diagnostic statements and their frequency were compared to the interpretations of the board certified cardiologist using an adaptation of the Minnesota code.

RESULTS

Of 212 subjects screened for the study, 38 were excluded for clinical reasons and did not have an ECG recorded. Of the remaining 174 subjects who had an ECG recorded, 24 (14%) were excluded because of abnormalities on the screening ECG. Of the 24 subjects that failed screening for ECG abnormalities, 17 were for ST or T wave abnormalities, 5 for arrhythmias or QT prolongation, 1 for right ventricular hypertrophy and 1 subject for first degree AV block. The remaining 60 subjects failed the screening clinical study entry criteria.

Among the 89 subjects, 803 ECG were recorded that included an occasional repeat tracing for lead reversal or artifact; 101 tracings were excluded for excessive artifact or a duplicate tracing for the time interval, and an additional 22 ECG that were otherwise interpretable were excluded for the ER analysis because of artifact that interfered with accurate J-point and ST segment measurements. Subjects' age ranged from 18–32 years (mean age 25). Fifty-seven (64%) were men and 32 (36%) were women. Eighty (88.9%) were white and 6 (6.7%) were black.

Suspect Cardiac Events

Thirty-two adverse events were evaluated specifically for possible cardiac related complications in 24 subjects during the follow-up period and included chest pain or tightness (11 events), dyspnea (3 events), nonspecific ST or T wave changes (15 events) and 1 transient Q wave change subsequently determined secondary to precordial lead transposition.[4] In addition 1 subject (discussed below) was classified as having possible myopericarditis (1 event) combined with a small pericardial effusion (1 event). Nineteen events occurred in IMVAMUNE® recipients, 10 events occurred in Dryvax® recipients and 3 events occurred in subjects receiving placebo. There were no subjects enrolled in the study that had an elevated cardiac troponin level at any time point. Among the 11 subjects with chest discomfort, the ECG findings were normal in 10; 1 subject had minor ST-T wave changes. Of the 89 subjects that had ECG follow-up, 13 subjects (14.6%) had new asymptomatic T wave abnormalities, 2 of

whom had concomitant ST segment depression, and 1 was reported twice for a T wave abnormality. Cardiology consultation was requested for 17 of the 25 subjects with suspect cardiac symptoms or new ECG findings. Echocardiograms were performed in 12 of the 17 and all were normal except for 1 subject. This subject complained of shortness of breath and limited chest pain 4 days after receiving Dryvax® and was found to have a congenital bicuspid aortic valve, compaction syndrome and a small pericardial effusion. Minor transient ST segment depression was noted (0.03mV) in lead III. Serial cardiac troponin levels were normal, and the subject was classified as experiencing a possible episode of myopericarditis.

Cardiologist Morphologic Assessment of the Follow-up ECG by Subject

The protocol excluded subjects with major ECG abnormalities at baseline (e.g. ST depression ≥ 0.05mV or T inversion ≥ 0.1mV) to avoid confounding the ECG diagnosis of myocarditis or pericarditis after enrollment. During follow-up, 2 subjects (2.2%) developed new ST segment depression ≥0.1mV (both were ≥ Minnesota code 4.3) and had concomitant T wave abnormalities. Of the 89 subjects, 14 (15.7%) developed new T wave abnormalities (all were ≥ Minnesota code 5.3). Incomplete right bundle branch block was noted in 1 subject (1.1%) at baseline that resolved and reoccurred during follow-up. New ER abnormalities not present at baseline occurred in 7 subjects (8.2%).

Cardiology Over-read of MUSE Follow-up ECG Interpretations

The MUSE 12SL program indicated “nonspecific ST wave abnormality” in 1 subject, “nonspecific ST-T wave abnormality” in 1 subject and “nonspecific T wave abnormalities” in 10 subjects (11.2%). The cardiologist downgraded both ST segment abnormality tracing to T wave abnormalities and rejected 2 of the 10 computer reported T wave abnormalities. The computer program identified “early repolarization” in 8 subjects, 2 of whom were reported as “ST elevation, consider early repolarization, pericarditis or injury.” Of the 8 ER cases, 3 were rejected by the cardiologist, and none were considered consistent with pericarditis or injury. A new “incomplete right bundle branch block” was reported by the computer in 5 subjects (5.6%); none met the criteria for a significant interval change. For 1 subject the computer reported, “cannot rule out anterior infarct.” The cardiologist negated the infarct diagnosis but noted an incomplete right bundle branch block pattern as noted above.

The GE 12SL computer program reported a total of 21 cardiac arrhythmias or conduction disturbances in 19 ECG from 16 subjects during follow-up. The arrhythmias were atrial fibrillation (n=2), premature atrial complexes (n=1), premature supraventricular complexes (n=1), premature ventricular complexes (n=6), fusion complexes (n=3), junctional rhythm (n=2), undetermined rhythm (n=3), and for conduction disturbances, first degree A-V block (n=1), and second degree A-V block (n=2). The cardiologist negated all 21 arrhythmia or conduction disturbance diagnoses. Amongst the 21 cases computer reported arrhythmia cases, marked sinus arrhythmia was present in 4 tracings and artifacts in 7 cases that may have caused the erroneous computer statement.

ECG Abnormalities during Follow-up

Table 2 illustrates new ECG abnormalities observed during the vaccination program, their temporal relationship to IMVAMUNE® or Dryvax® vaccination, and the percent of ECG abnormalities in each vaccination Group and by vaccination number. Group 1 received 2 doses of IMVAMUNE® followed by 1 dose of Dryvax®. Group 2 received saline placebo for the first 2 vaccinations followed by Dryvax® and serves as a Dryvax alone control. Group 3 received 2 doses of MVA followed by saline placebo and served as the MVA alone control. Despite small numbers, there were no apparent differences in interval ST or T wave changes between the control and IMVAMUNE® treatment groups.

DISCUSSION

The US Department of Defense (DoD) and DHHS Smallpox Vaccination Program used full-strength concentration of smallpox vaccine (Dryvax®, Wyeth Laboratories, Marietta, PA) for healthy military and potential first responder emergency personnel to protect against a bioterrorism attack. Concerns about Dryvax® vaccine complications such as encephalitis and myocarditis have led to the development of less virulent strains that can provide protection to a general civilian population. The second vaccine used in this study (IMVAMUNE®) was derived from an attenuated MVA strain. Cardiac surveillance guidelines that describe case definitions for smallpox vaccine adverse reactions include clinical symptoms, ECG changes, abnormal cardiac biomarkers, abnormal cardiac imaging studies, or histopathological findings.[7] Of 540,824 subjects vaccinated from December 2002–December 2003 in the DoD program, 67 (1/10,000) reported chest pain or substernal pressure and were diagnosed with myopericarditis approximately 10–21 days after vaccination.[1] Of the 61 subjects with available ECG data, 46 (75%) had ECG abnormalities, most commonly ST-T wave abnormalities, including ER; only 2 subjects had PR depression. The ECG reverted to baseline in all but 1 case after a median of 108 days after initial presentation.

We did not observe major PR depression in any of the volunteers in this study. In our sample of 89 subjects ≤ 32 years of age, new post-randomization T wave abnormalities occurred in 15.7% of subjects and ST segment abnormalities in 2.2% of subjects during the 26 weeks of follow-up; the abnormality resolved on subsequent ECG tracings in 71.4% of cases. The prevalence of minor Minnesota code T wave abnormalities is 1–3% in apparently healthy subjects < 30 years.[8,9] The likelihood of detecting new ST-T wave abnormality is enhanced when many ECG are acquired over time since a carbohydrate load, electrode position, hyperventilation and electrolyte abnormalities can induce minor repolarization changes.[10] Serial ECG follow-up of apparently healthy populations reveals transient ECG abnormalities that are more common in older subjects, particularly in the presence of atherogenic risk factors. In the Chicago Western Electric Study of 1673 men aged 40–55 years without evidence of coronary heart disease or major ECG abnormalities at baseline, 105 (6.3%) had evidence of minor Minnesota code ST-T wave abnormalities in 1 of numerous ECG acquired during long-term follow-up.[11] In other similar studies of middle-aged men, the prevalence of abnormal ST-T wave abnormalities ranges from 6–10%.[12]

The diagnostic accuracy of the ECG to detect subclinical myocardial ischemia, myocarditis or pericarditis is limited in a population < 40 years. Myocardial ischemia is uncommon in individuals < 40 years and symptomatic myocarditis or pericarditis occurs in only 1:10,000 subjects after vaccination with the NYCBOH vaccine.[1] Since the incidence of benign repolarization abnormalities in apparently healthy volunteers may approach 10–20% with multiple ECG sampling, one might expect from Bayesian principles that new minor repolarization abnormalities are much more likely to be a false positive for the diagnosis of cardiac pathology than a true positive. Indeed, using the above numbers, the predictive value of a new minor repolarization abnormality to detect myopericarditis is < 1%. Of the 89 subjects enrolled in this series, protocol required serial troponin measurements in all subjects were within normal range. Nevertheless, the ECG is a useful tool to exclude subjects with underlying cardiac disease prior to vaccination and to evaluate symptomatic episodes where the likelihood of a cardiac event, i.e. pericarditis, myocarditis, myocardial ischemia is increased.

We compared computer assisted ECG interpretations to those of a board certified cardiologist to determine if the computer readings alone could serve as a tool to determine if additional cardiology follow-up procedures were necessary in this population of vaccinated subjects. The frequency of false positive diagnoses for cardiac arrhythmias was excessive, a finding previously described, and the type and description of repolarization abnormalities unreliable

for general use in a vaccination program by non-cardiologists where the ECG reading is done by less experienced ECG readers.[13,14] Erroneous computer statements or misinterpretation could lead to inappropriate referrals to a cardiologist and unnecessary additional testing that would not be cost-efficient.

ER abnormalities are common and can confound the diagnosis of ischemia or myopericarditis and lead to unnecessary cardiology work-up in a vaccination program in a young population.[3,15–21] We used a strict definition for early repolarization compared to the Wasserburger definition for example because this population was <40 years old.[6,17] The PQ junction was used to determine J-point and ST segment offsets in the absence of major PR depression as recommended by the Centers for Disease Control (CDC).[1,5]

In conclusion, the use of frequent ECG tracings to screen individuals < 40 years of age enrolled in a smallpox vaccination program to detect subclinical cases of myocardial ischemia or myopericarditis is not efficient since most ECG abnormalities that occur after vaccination are minor and unlikely to be caused by underlying cardiac pathology. For healthy subjects < 40 years of age receiving Dryvax® (replicating virus in humans) and all subjects receiving MVA (nonreplicating virus in humans) in clinical trials, an ECG prior to vaccination is recommended to exclude subjects with significant cardiac pathology and to be used as a baseline reading to evaluate cardiopulmonary symptoms post randomization should they occur after vaccination.. For clinical trials in subjects > 40 years of age where the prevalence of occult coronary disease is more common and who receive doses of Dyvax or other vaccinia that replicates in humans one might consider an additional ECG 10–14 days post-vaccination during the period when the majority of symptomatic cardiotoxic effects have been observed. These recommendations could change as experience with MVA accumulates.

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Table 1

MID 02-017 Vaccination Schema

Groups for the ECG Analysis	Main Study Groups	Number of Subjects	MVA Dose	Route*	Day 0	Day 28 (Week 4)	Day 112 (Week 16)
1	A	15	2×10^7	SC	MVA	MVA‡	Dryvax®†
	B	15	5×10^7	SC	MVA	MVA‡	Dryvax®†
	C	15	1×10^8	SC	MVA	MVA‡	Dryvax®†
	F	15	1×10^8	IM	MVA	MVA‡	Dryvax®†
2	D	15	N/A	SC	Placebo**	Placebo**	Dryvax®†
3	E	15	1×10^8	SC	MVA	MVA‡	Placebo**

*SC=subcutaneous, IM=intramuscular

†1×10^8 plaque forming units (pfu)

‡Tissue culture infective dose 50 ($TCID_{50}$)

**The placebo is sterile normal saline

Table 2

Subjects with New ECG Abnormalities after Vaccinations

Events	Groups	After 1st vaccination* n (%)	After 2nd vaccination† n (%)	After 3rd vaccination‡ n (%)	Total
ER	1	0 (0.0)	3 (5.2)	2 (4.2)	5
	2	0 (0.0)	0 (0.0)	1 (7.7)	1
	3	0 (0.0)	1 (7.7)	0 (0.0)	1
ST segment abnormality	1	0(0.0)	0(0.0)	1 (2.1)	1
	2	1 (6.7)	0 (0.0)	0 (0.0)	1
	3	0 (0.0)	0 (0.0)	0(0.0)	0
T wave abnormality	1	4(7.0)	3(5.2)	2 (4.2)	9
	2	2 (13.3)	1 (7.1)	1 (7.7)	4
	3	0 (0.0)	0 (0.0)	1 (11.1)	1
All abnormalities	1	4 (7.0)	6 (10.3)	4 (8.3)	14
	2	2 (13.3)	1 (7.1)	2 (15.4)	5
	3	0(0.0)	1(7.7)	1 (11.1)	2
Number of subjects completing each vaccination	1	60	59	50	
	2	15	14	13	
	3	15	14	9	
Subjects with analyzable ECG**	1	57	58	48	
	2	15	14	13	
	3	14	13	9	

* = visit 6 and 7

† = visit 11, 12, and 13

‡ = visit 14, 15, and 16

** ECG with excess artifact were excluded for analysis. Subjects with at least 1 analyzable ECG during the period were counted. Subjects were not counted after they missed the vaccination.

Group 1: IMVAMUNE®, IMVAMUNE®, Dryvax®

Group 2: Placebo, Placebo, Dryvax®

Group 3: IMVAMUNE®, IMVAMUNE®, Placebo

Total ECG event category is not mutually exclusive

ER=early repolarization; ER was not reported as adverse event.

Additional 1 repeated T wave abnormality was reported as adverse event.