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Agent Orange and ischemic heart disease: Long-term consequence for Vietnam Veterans

Richard E Katholi

Prairie Educational Research Cooperative and Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, Illinois, USA

Abstract

Agent Orange was a powerful herbicide mixture used by U.S. military forces during the Vietnam War to eliminate forest cover protecting enemy troops. Much of Agent Orange contained a dangerous chemical contaminant called dioxin. An important dioxin-mediated effect on humans is causing endothelial dysfunction. If endothelium is dysfunctional and not producing normal amounts of nitric oxide, premature atherosclerosis can occur and progress. The Veterans Administration has acknowledged that Agent Orange is a risk factor for coronary artery disease. When seeing patients, it is important to determine if they served in Vietnam during the period of Agent Orange spraying. It is recommended these Veterans have aggressive coronary risk factor modification with long-term followup.

Keywords: *Agent Orange, dioxin, endothelial dysfunction, coronary artery disease, ischemic heart disease*

Agent Orange and ischemic heart disease: Long-term consequence for Vietnam Veterans

Agent Orange was a powerful herbicide mixture used by U.S. military forces during the Vietnam War to eliminate forest cover protecting enemy troops, North Vietnamese and Viet Cong troops [1-3]. The U.S. program, code-named, "Operation Ranch Hand," sprayed more than 20 million gallons. The "Agent Orange" name comes from the fact that the containers holding the herbicide had a broad orange stripe on them. The country of Vietnam was a long narrow country. The U.S. and allies were supporting the South Vietnamese. There were supply lines and troop areas called "Ho Chi Minh trails." This area had much jungle and canopy-type forests, and the concept was to defoliate these areas as best as possible to allow for better visibility during bombing raids. Much of Agent Orange contained a dangerous chemical contaminant called dioxin [4]. Dioxin is a contaminant formed in the production of some chlorinated organic compounds, including herbicides. The number of chlorine atoms and their positions in the dioxin molecule are what determines the toxicity of different dioxins. The herbicide was sprayed from C-123 aircraft. This activity was carried out over many years from an air base, Bien Hoa. In the 1990s or 20 years after the end of the Vietnam War, studies have been carried out in the Bien Hoa area to determine the fate of dioxin. Blood samples from local inhabitants were often strikingly high, and on further evaluation, it was determined that runoff resulted in dioxin in the sediment in the rivers. The dioxin got into fish and then the fish were consumed by humans, and that is why the levels in some citizens were so high [5].

Dioxins have been shown to have many effects on humans [5]. One important effect of dioxins is causing endothelial dysfunction, the consequences of which include coronary artery disease and type 2 diabetes [6]. Endothelial dysfunction is the focus of this review. Dioxins also produce alterations in the immune system, and mentioning possible consequences from dioxin's toxic effects on the immune system is warranted.

Agent Orange has caused many long-term problems in individuals who were exposed. This includes, not only the American troops, but the local inhabitants of Vietnam. The spraying went from January 9, 1962 through May 7, 1975. Any Veteran who was in Vietnam during that time has the potential of having been exposed to Agent Orange [6].

Diseases from Agent Orange exposure acknowledged for compensation by the Veterans Administration include those that occurred within a year of exposure to Agent Orange [6]. Skin diseases included exacerbation of porphyria cutanea tarda and also an acneiform disease. These responses, if they occurred, were self-limiting. Another more acute effect was a subacute peripheral neuropathy which occurred in exposed individuals within a year of exposure but was self-limiting and had resolved within two years. Thus, these more acute effects are no longer a problem for Veterans.

Diseases from Agent Orange exposure acknowledged for compensation by the Veterans Administration include B-cell leukemias, lymphocytic leukemia, multiple myeloma, soft tissue sarcoma, prostate cancer, Hodgkin's disease and non-Hodgkin's lymphoma, all thought to be a problem with the immune system. Also, there are respiratory cancers, including lung, larynx, trachea and bronchus, from inhaled toxicity. Other late neurological diseases include Parkinson's disease [6].

During the years of Agent Orange spraying, over 7 million troops were in country. It is considered that 3 million are at particularly high risk due to their location in the country and their assignments [1]. The Vietnam War was different than World War I, World War II or the Korean War in that there were not major

fronts with battle lines. The South Vietnamese and allies controlled the bases, controlled cities and were trying to control the hamlets, but the countryside of Vietnam, which the GI's referred to as "the bush," was an area where North Vietnamese troops, Viet Cong and allies had interactions. The strategies included search and destroy missions, and nerve-racking and spooky aspects of search and destroy missions were well demonstrated in the movie, "Platoon." Infantry in "the bush" was in combat almost continuously-harassed by enemy mines, booby traps and snipers, if not engaged in direct clashes [2,3]. For the troops in more Northern areas of the country, they were exposed to direct spraying from the C-123's dispensing Agent Orange. I have patients who remember being out in the bush, the planes flew overhead, and the herbicide rained down on not only the plants but also the troops resulting in significant exposure [3].

Over the years, Vietnam Veterans exposed to Agent Orange are being found to have premature and extensive coronary artery disease. Ischemic heart disease from Agent Orange exposure is acknowledged for compensation by the VA [6]. Another occupation that increases the risk of endothelial function because of ionizing radiation is being an astronaut. Most astronauts have developed significant coronary disease later in life. The risk of endothelial dysfunction from ionizing radiation has also been observed in patients with Hodgkin's disease treated with mantle radiation.

The bottom line is whether it is ionizing radiation or Agent Orange or smoking, the endothelium controls the destiny of the cardiovascular system. If the endothelium is dysfunctional and not producing normal amounts of nitric oxide, premature atherosclerosis can occur and progress. A recent article discussing the effects of cancer chemotherapy on the heart includes the fact that anthracycline can also cause endothelial dysfunction [7]. An editorial states, "You are only as good as your endothelium" [8].

We need to identify patients whose endothelium has been damaged, whether it be by smoking, Agent Orange, ionizing radiation or anthracycline therapy, and try to improve endothelial function by aggressive evidence-based goals. These patients should no longer smoke. Regular aerobic exercise, lowering blood pressure to 130/80 mmHg or better, lowering LDL cholesterol to less than 70 mg/dL, triglycerides to less than 150 mg/dL and lowering hemoglobin A1C to less than 7%, all have been shown to improve endothelial function [9,10]. A medication which would be a good choice in patients with ischemic heart disease is carvedilol. Carvedilol which has very strong antioxidant effects has been shown to decrease microalbuminuria in hypertensive diabetic patients. The interpretation of this finding is because the endothelium of the glomerular apparatus has been improved through the antioxidant effects of carvedilol [11]. Carvedilol also is a good choice in these patients because compared to metoprolol tartrate, carvedilol decreases insulin resistance while metoprolol worsens it. Carvedilol is weight-neutral while metoprolol tartrate and other beta-blockers result in patients gaining approximately 2 pounds every six months. Carvedilol also is triglyceride-neutral while metoprolol tartrate and other beta-blockers increase triglycerides by about 13% [11].

In dealing with these patients, thus, carvedilol is recommended. Weight loss is recommended through calorie restriction and exercise. Regular exercise increases insulin sensitivity and decreases the risk for type 2 diabetes. It has been shown that the combination of antioxidant supplements, vitamin C and vitamin E, blunt exercise-induced improvement in insulin sensitivity [12]. Thus, it is recommended that these patients not take these antioxidant substances. A proven antioxidant, thus far, is carvedilol. Weight reduction not only lowers blood pressure, improves cholesterol profile and lowers hemoglobin A1C, but weight loss also decreases the tendency toward sleep apnea and improves patients with fatty liver. Besides increasing cardiovascular risk from hypertension, cigarette smoking also facilitates progression of renal disease, particularly in diabetic patients. A recommended diet, such as the DASH diet, not only has sodium restriction but contains fruits, vegetables and grains which contain arginine [10]. Arginine is the substrate for the endothelium's ability to synthesize nitric oxide. Two foods that are particularly high in arginine include sesame seeds and soy protein [8]. Benefits of lowering blood pressure include decreasing stroke incidence by 35-40%, decreasing myocardial infarction by 20-25% and decreasing the risk of heart failure by 50% [10].

In summary, Agent Orange exposure should be considered a risk factor for coronary artery disease. Identifying patients who were exposed to Agent Orange is important. It is recommended when seeing patients to ask whether they are Veterans and if they served in Vietnam during the period of Agent Orange spraying. If they fit that criteria, Agent Orange should be considered a risk factor for coronary artery disease, and it is recommended these patients have aggressive coronary risk factor modification with long-term followup.

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Correspondence: Richard E Katholi, Prairie Cardiovascular Consultants, Ltd., P.O. Box 19420, Springfield, IL 62794-9420, USA; Email: rkatholi@aol.com

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