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Review article

Exploring exposure to Agent Orange and increased mortality due to bladder cancer

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Abstract

Background: During the Vietnam War, many veterans were exposed to Agent Orange (AO), a chemical defoliant containing varying levels of the carcinogen dioxin. The health effects of AO exposure have been widely studied in the VA population. Here we review and interpret data regarding the association between AO exposure and bladder cancer (BC) mortality.

Main findings: Data evaluating the association between AO and BC is limited. Methods characterizing exposure have become more sophisticated over time. Several studies support the link between AO exposure and increased mortality due to BC, including the Korean Veterans Health Study.

Conclusions: Available data suggest an association with exposure to AO and increased mortality due to BC. In patients exposed to AO, increased frequency of cystoscopic surveillance and potentially more aggressive therapy for those with BC may be warranted but utility of these strategies remains to be proven. Additional research is required to better understand the relationship between AO and BC.

Keywords: Agent Orange; 2,3,7,8-Tetrachlrododibenzo-p-dioxin (TCDD); Environmental exposure; Bladder cancer; Mortality; Exposure assessment

1. Introduction

From 1961 to 1971 the United States (US) military used chemical herbicides in "Operation Ranch Hand" during the Vietnam War [1,2]. These tactical mixtures were used as a chemical defoliant often to clear perimeters of military bases and improve visibility [1]. In total, 77 million liters of numerous chemical defoliants were used [1]. Of these agents, the most commonly used herbicide was Agent Orange (AO). Although many studies have examined the health effects of AO [3–7], the relationship between AO and bladder cancer (BC) mortality is less well studied. Of the data that is currently available in this area, a few studies suggest higher BC mortality associated with AO. qAs a result, attentive screening and aggressive upfront therapy for patients with this history of potential exposure could possibly be efficacious and warranted. More research is needed to further elucidate the relationship between AO and BC and to determine the best screening and treatment protocols.

2. BC is common and costly

In addition to the clear adverse health consequences of BC, it also poses a substantial societal and financial burdens. BC is often diagnosed by painless gross hematuria and transurethral resection to verify pathologic stage [8]. Veterans of the Vietnam War are now in the most common age group for a BC diagnosis, typically first diagnosed when a patient is in their 70s [9]. Exploring the effect of AO in BC, is particularly relevant to this population and also other individuals potentially exposed to AO including Vietnamese civilians. BC is the fourth most common cancer in men, with over 15,000 deaths in 2015 alone [10].

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Smoking is a well-established risk factor and occupations associated with increased risk include jobs with exposure to chemicals including textile manufacturing, rubber processing, and dyestuff industry [11]. BC is the one of the most expensive cancers per patient to treat, with estimated costs at $200,000 per patient, translating to $3.6 billion per year in expenditures [12].

3. Exposure description and toxicokinetics

AO is composed of varying amounts of dioxin, a known carcinogen [3]. Approximately, 65% of all herbicides used during the Vietnam War contained 2,4,5-tricholorophenoxyacetic acid (2,4,5-T), which was contaminated with varying levels of 2,3,7,8-tetrachlrododibenzo-p-dioxin (TCDD) [1], an unwanted byproduct. Data studying the harmful effects of 2,4,5-T are limited and the toxicity originally attributed to 2,4,5-T were later shown to be partially due to TCDD [3]. AO, is composed of both 2,4,5-T and 2,4-D, and contains varying levels of TCDD, one of the most well studied and toxic compounds from that conflict [3,13,14]. Concentration of TCDD in mixtures has varied from 3 to 32 parts per million (ppm), making it difficult to standardize contamination levels [15]. Review of updated Herbicide Report System files [16], core soil samples from test flights in Thailand, records of sorties by military crews, and census data from flight path frequency grids in Vietnam have led to a more precise understanding of spraying patterns and have estimated an average contamination value of 13 ppm of TCDD within barrels of AO [15].

Soldiers may have been exposed to AO via multiple routes. Although ordinances to protect soldiers were in place, veterans may have had direct exposure while handling the liquid herbicide or have been sprayed directly resulting in dermal contact and inhalation [17–19]. For other soldiers (particularly infantry), walking through previously TCDD contaminated environments led to biological exposure predominately via contact with bare skin in densely sprayed areas [17–19]. Studies of absorption have shown TCDD concentrations are decreased by photolysis when exposed to light. Studies with human volunteers receiving 2 hours of bare skin contact showed levels of 0.15% to 0.46% of one of the active metabolites of AO (2,4,5-trichloropheonxyacetic acid) entered the body and were excreted in the urine [19]. After absorption, TCDD is distributed primarily to the liver and body fat. Excretion of this metabolite in the urine, with direct contact with the bladder epithelia, suggests a mechanism for carcinogenic effects in BC, similar to other elements such as arsenic and aromatic amines, that are excreted in the urine and are causally associated with BC [8,20].

The half-life of TCDD in humans has been reported to be between 1.1 and 7.8 years in adults depending in part on the amount of exposure and timing of measurement [3]. The poisoning of a Ukrainian presidential candidate, Victor Yushchenko, in 2004 with TCDD provided a single, study of human toxicokinetics [21]. Over a 1-year period 38% of the TCDD was eliminated as metabolites and 62% as the parent chemical. Of the eliminated metabolites, 5% was excreted in the urine (as 2,3,7-trichloro-8-hydroxydibenzo-p-dioxin and 1,3,7,8-tetrachloro-2-hydroxydibenzo-p-dioxin) [21]. In this case report, the half-life of TCDD was found to be 15.4 months at 3 years of follow up.

4. Exposure assessment

Since the concentration of TCDD is in the lipid fraction of serum which is in equilibrium with tissue stores (such as adipose), serum concentrations can be used to estimate total body burdens [3]. Studies of pharmacokinetics in adult males who participated in operation Ranch Hand used serum TCDD levels to determine half-life and effect of body fat on metabolism [22–25]. A 15-year study of Ranch Hands identified a half-life of 7.6 years (95% CI: 7–8.2 years) and found that the elimination rate decreased significantly with increasing body fat [23]. Estimates of TCDD half-life have been extensively studied in both humans and animals and toxicokinetic studies have shown variability with age, sex, and body mass index [3]. However, measuring TCDD is influenced by multiple factors including the type of tissue examined, the nature of exposure, timing since the exposure, and adipose tissue mass [3,22–24]. Despite these limitations, evaluation of TCDD levels remain one of the most commonly studied methods for assessing AO exposure.

Given the variability of AO exposures, and limitations with biological monitoring, it has been difficult to accurately determine level of exposure in individuals, and consequently, associations with health outcomes [26]. The Agent Orange Act of 1991 addressed this problem by asking the National Academy of Science (NAS) to examine the association of AO exposure on health [2]. This led to the development of an updated framework for categorizing exposure known as the Geographic Information System (GIS) [27]. GIS used Herbicide Report System records aircraft flight paths, gallons used, locations of military units, movement dynamics of troops, and locations of civilian centers to revise estimates and models quantifying exposure to AO. These are often updated as more historical data become available [27–29]. The GIS is built upon complex spatial and temporal algorithms to create exposure opportunity indexes that better capture exposure for soldiers in Vietnam. This mathematical modeling harnesses detailed civilian and military data to create a “grid” over geographic locations in Vietnam to inform intensity of exposure.

Further reasons supporting the creation of the GIS exposure opportunity indexes is the inadequacy of biological monitoring tests to accurately characterize exposure, as evidenced by earlier works has reporting no clear difference in serum levels among those who sprayed, or