Hypertension and Persistent Organic Pollutants in the Anniston Community Health Survey Follow-up

Pavuk M[1], Yang E[2], Lewin M[1], Birnbaum LS[3]

[1]Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC), Atlanta, GA;
[2]ORISE and ATSDR, CDC, Atlanta, GA;
[3]National Cancer Institute, NIH, Research Triangle Park, NC;

Introduction

From 1932 to 1971, Anniston, Alabama was the site of a former Monsanto Chemical Company production facility that manufactured polychlorinated biphenyls (PCBs). The products consisted of commercial and experimental Aroclor® mixtures. Each contained various PCB congeners, which accounted for over half of the total PCB production in the U.S. Elevated PCB concentrations have been measured in both the environment and people [1,2]. We have previously reported on PCB exposure and hypertension in Anniston residents of the Anniston Community Health Survey (ACHS 2005-7) [3]. Among ACHS individuals not taking antihypertensive medication, we found a significant association between sum of 35 ortho-substituted PCBs and hypertension; we also found a positive correlation between PCBs and blood pressure levels (both systolic and diastolic) [4]. In 2014, we conducted a follow up of ACHS (ACHS II), in which dioxins and dioxin-like non-ortho PCBs were added to the analytical plan to expand on the exposure profile of the Anniston cohort [5].

Associations between exposures to persistent organic pollutants (POPs) and hypertension have been studied extensively. Various studies have revealed a connection between chemicals such as dioxins, furans, PCBs, and pesticides, and hypertension [6,7,8]. Meta-analyses have shown that dioxin-like PCBs are more likely to have a significant association with elevated hypertension risk than non-dioxin-like PCBs [9]. We present the results of ACHS II showing the relationship between various persistent organic pollutants, including dioxin-like compounds, and hypertension.

Materials and Methods

Study Design and Population

Methods for the ACHS and ACHS II were described elsewhere in detail [2,5]. All surviving ACHS I participants with PCB measurements were eligible to participate in the follow up. Prior to enrollment, we managed to attain mortality status on 114 participants and found that 69 participants moved to distant addresses outside the study area. We successfully contacted the remaining 438 participants (with the current address in the study area). Of those, 359 participants enrolled in the follow up study. They provided a fasting blood sample for measurements of glucose, PCBs and lipid levels, and had their height, weight, waist circumference, and blood pressure measured using a standardized protocol. Demographic information, medical and family history, as well as self-reported health behaviors, health

conditions, occupations, and individual medications were also recorded. Of the 359 enrolled participants, 338 had sufficient serum for dioxin analyses and provided covariate information, and were included in the statistical analyses. The studies were reviewed and approved by the appropriate Institutional Review Boards.

Laboratory and Statistical Analyses

Generally, 18 mL to 20 mL of sera were collected from each individual for dioxin analyses. After blood samples were centrifuged, the sera were aliquoted and stored at -20°C until shipment. Once the samples were shipped to the laboratory, they were stored at -70°C until analyzed. Seven PCDD, ten PCDF, and three no-PCB congeners (PCBs 81, 126, and 169) were measured in the sera by the Centers for Disease Control and Prevention's National Center for Environmental Health laboratory. The analytes were separated on a DB-5 MS capillary column (Rxi 5Sil MS; Restek, Bellefonte, PA) and quantified with selected ion monitoring, high-resolution (10,000 resolving power) mass spectrometry [12]. The 35 major ortho- and mono-ortho-substituted PCB congeners were measured by the same laboratory using high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry in both studies as described previously [13]. Triglyceride and total cholesterol measurements were used in the enzymatic "summation" method to calculate serum total lipids [14]. The congeners' toxic equivalency (TEQ) and total dioxin TEQ were calculated from the 2005 WHO Toxic Equivalency Factors (TEF) [15]. For the particular sum of TEQs, only congener concentrations above the limit of detection for each individual were used in the summation.

Hypertension was defined as being on antihypertensive medication or having a systolic blood pressure greater than 140 mmHg and/or a diastolic pressure greater than 90 mmHg [3,4]. Blood pressure was measured by a nurse with a standard sphygmomanometer, arm cuff, and stethoscope in 2-minute intervals after the participant had been sitting for five minutes. Logistic regression models were used to analyze hypertension status (hypertensive, non-hypertensive) with the exposure variables: total dioxin TEQ and its subcomponents (PCDD TEQ, PCDF TEQ, mono-ortho PCBs TEQ and non-ortho PCBs TEQ) [15]. For these analyses, the non-ortho PCBs TEQ was the sum of PCB 126 TEQ and PCB 169 TEQ; only 3.4% of participants had PCB 81 above the method's limit of detection. These congeners were also modeled separately as elevated concentrations were reported in some Anniston residents. Other covariates in adjusted logistic regression models included age, race (African-American or White), sex (female or male), BMI (continuous), current smoking status (yes or no), and family history of high blood pressure. Odds ratios (OR) and 95% Confidence intervals (CI) are presented.

Results and Discussion

High prevalence of hypertension (78%) was observed in the follow up sample of Anniston cohort. Participants with hypertension were older by about 8 years. There was a significantly higher proportion of African Americans in the hypertensive group (56% vs. 33%). The majority of the sample consisted of women (72%) and were obese (59%). Total lipids and smoking status did not differ significantly by hypertensive status.

Table 1. Demographics of ACHS II stratified by hypertensive status.

Demographics	Hypertensive (n=263)	Non-hypertensive (n=75)
Age (years)*	64.46 ± 0.73	56.39 ± 1.77
BMI (kg/m^2)	31.97 ± 0.51	30.50 ± 0.90
Total lipid (mg/dL)	623.72 ± 9.83	620.01 ± 16.16
Girth (inches)	42.12 ± 0.38	41.03 ± 0.75
High Blood Pressure Family History	208 (79.09%)	53 (70.67%)
Age Categories (years)*		
<40 years	8 (2.37%)	11 (3.25%)
40-59 years	83 (24.56%)	35 (10.36%)
≥60 years	172 (50.89%)	29 (8.58%)
BMI Categories (kg/m^2)*		
Normal Weight (<25 kg/m^2)	47 (13.91%)	21 (6.21%)
Overweight (25-29.99 kg/m^2)	70 (20.71%)	26 (7.69%)
Obese (≥30 kg/m^2)	146 (43.20%)	28 (8.28%)
African Americans*	147 (55.89%)	25 (33.33%)
Females	193 (73.38%)	52 (69.33%)
Smoking Status (yes)	56 (21.29%)	15 (20.00%)
Lipid Lowering Medication*	123 (36.39%)	13 (3.85%)

*Statistical difference between hypertensive and Non-hypertensive individuals (p-value<0.05)

Table 2. OR (95% CI) of Hypertension Prevalence in ACHS II participants.

		Unadjusted		Adjusted	
TEQ (pg/g lipid)	n*	OR (95% CI)	P-value	OR (95% CI)	P-Value
PCDD	262/337	6.08 (2.40, 15.42)	0.0001	1.28 (0.32, 5.03)	0.73
PCDF	261/336	5.66 (1.98, 16.20)	0.0012	1.52 (0.39, 5.92)	0.55
Mono-ortho PCBs	263/338	4.14 (2.42, 7.07)	<0.0001	1.57 (0.66, 3.73)	0.31
Non-ortho PCBs	251/313	2.98 (1.66, 5.35)	0.0003	1.82 (0.84, 3.92)	0.13
Total Dioxin	263/338	5.78 (2.62, 12.74)	<0.0001	1.27 (0.41, 3.97)	0.68

Each logistic regression model was adjusted for age, sex, race, BMI, family history of high blood pressure, and smoking status. . *n=#hypertensive/total

We analyzed TEQ groups and hypertension status with unconditional logistic regression models. Strong associations between TEQ groups and hypertension were observed (OR and CI) . For unadjusted analyses magnitude of the association was strongest for the PCDD TEQ and total dioxin TEQ (ORs: PCDD>PCDF>mono-ortho PCBs> non-ortho PCBs). Adjustment for hypertension risk factors substantially attenuated the strength of association for all TEQ groups, but the direction of association still indicated elevated odds (OR 95% CI). For PCDD TEQs the OR=6.08 dropped to OR_{adj}=1.28; other adjusted ORs saw a similar change except for non-ortho PCBs TEQ where the drop in odds ratios was the least pronounced (OR=2.98, adjusted OR_{adj}=1.82). In the adjusted models, the non-ortho PCBs had the highest ORs. Although not statistically significant by conventional hypothesis testing criteria, adjusted ORs were above 1.5 for non-ortho and mono-ortho PCBs as well as for PCDF TEQs, and confidence limits ranging from 0.3 to 5.92 suggest that these data are more compatible with moderate association than with no association among hypertension and dioxin-like compounds, assuming the statistical model used is correct and is

absent of bias. These estimates are similar to those reported in previous studies and in line with the results of recent meta-analyses [6,7,8,9].

The first Anniston study reported elevated odds ratios for sum of PCBs for hypertension and for di-orhto and tri-tetra-ortho congeners with increasing blood pressure [3,4]. When analyzing all the chemicals by individual congeners in the follow up study (not shown in the table), we found that PCBs and pesticides had stronger associations with hypertension than associations between PCDD/F congeners and hypertension (which were weaker and did not reach significant associations with the health outcome). Strongest associations were observed with non-dioxin like PCBs, di-ortho congeners 99 (OR=2.03 (95% CI 1.01, 4.06)) and 138 (OR=2.36 (95% CI (1.05, 5.30)) which were similar in magnitude to non-ortho PCBs 126 and 169. Among pesticides, we found highest estimates for oxychlordane (5.05 (1.28, 19.83)) and *trans*-nonachlor (4.73 (1.45, 15.41)) to have a strong association with hypertension.

In the Anniston follow up study we continue to see elevated odds ratios for hypertension with PCBs, both for dioxin-like non-ortho PCBs (including TEQs) and non-dioxin-like PCB congeners [3,4]. In addition, strong association with some chlorinated pesticides were reported (oxychlordane: OR= 5.05 (1.28, 19.83) and *trans*-Nonachlor: 4.73 (1.45, 15.41)), which was not seen in the first study. Dioxins and furans also showed associations with hypertension but weaker than PCBs and pesticides (data not shown). These analyses focused on contrasting those with hypertension and those without hypertension, as over 75% of the cohort was hypertensive in 2014 (about 51% was on anti-hypertensive medication at 2005-7 examination). Hypertension and exposures to persistent POPs continue to be of concern in this population.

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