Environmental Research 135 (2014) 70–75

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Perfluorocarbons and Gilbert syndrome (phenotype) in the C8 Health Study Population

Hongmin Fan [a,b,*], Alan Ducatman [c,d,e,*], Jianjun Zhang [f]

[a] Cancer Center, School of Public Health, West Virginia University, Morgantown, WV 265050-9190, USA
[b] Department of Epidemiology and Statistics, School of Public Health, Hebei United University, Hebei 063000, PR China
[c] Department of Occupational and Environmental Health, School of Public Health, West Virginia University, USA
[d] Department of Medicine, School of Medicine, West Virginia University, USA
[e] Clinical Translational Science Institute, West Virginia University, USA
[f] Department of Biostatistics, School Public Health, West Virginia University, USA

ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form
3 August 2014
Accepted 11 August 2014
Available online 28 September 2014

Keywords:
Perfluorocarbon
Perfluorohexanoic acid (PFHxA)
Perfluorooctanoic acid (PFOA)
Perfluorooctanesulfonate (PFOS)
Bilirubin
Gilbert syndrome

ABSTRACT

Background: Gilbert syndrome (GS) is an inherited defect of bilirubin conjugation, most commonly caused by a gene mutation for the enzyme UGT1A. GS is known to affect the metabolism and excretion of drugs and xenobiotics. Perfluorocarbon compounds (PFCs) are bio-persistent environmental contaminants that affect metabolic regulation. In this study, we examined the associations of GS phenotype and serum PFCs in the C8 Health Study Population.

Materials and methods: Using 2005–2006 data from a large PFC-exposure population survey, we compared serum PFCs concentrations between GS and non GS clinical phenotypes, in a cross sectional design, adjusting for standard risk factors, including age, BMI, smoking status, socioeconomic status and gender.

Results: Among 10 PFC compounds considered, only perfluorohexanoic acid (PFHxA) was seen at a significantly higher concentration in GS men and women.

Conclusion: PFHxA exposure may be associated with GS. Our findings do not support increased exposure in GS for other PFCs.

1. Introduction

Our study goal was to evaluate whether individuals who exhibit the Gilbert syndrome (GS) phenotype also retain more perfluorocarbon compounds (PFCs) in their serum. GS is most often caused by an inherited deficiency in the bilirubin-conjugating enzyme uridine-diphosphoglucuorysl-transferase 1A1 (UGT1A1); it is clinically characterized as unconjugated (indirect) hyperbilirubinemia in the absence of hepatocellular disease or hemolysis (Clementi et al., 2007). GS is regarded as a generally benign condition, and clinical recognition is often incidental to routine laboratory investigation. A homozygous genotype is present in about 10%, of Caucasians, but the frequency and specific abnormalities vary among populations, and homozygous individuals do not always express the phenotype (Rodrigues et al., 2012; Bosma et al., 1995). Renewed focus on the condition has followed from recognition that antioxidant properties of bilirubin may protect against age-related diseases; lower risks of cardiovascular and other vascular disease have been reported in diverse populations with the UGT1A1 variation (Vitek and Schwertner, 2007; Perlstein et al., 2008; Hopkins et al., 1996). However, the condition may also create exposure risks. Drugs and xenobiotics needing UGT1A1-mediated glucuronidation for elimination may accumulate in GS (Sticova and Jirsa, 2013). Our interest in the interaction of Gilbert's syndrome with perfluorocarbon compounds (PFCs) was prompted by the physiologic observation that organic anion transporter polypeptides (OATPs) are affected in Gilbert's syndrome along with the activity of UGT1A1 (Sticova and Jirsa 2013; McCarty, 2007; Persico et al., 2001), suggesting non-glucuronidation mechanisms for the accumulation of drugs and xenobiotics in GS.

PFCs are xenobiotic compounds widely used to manufacture industrial and popular consumer products such as nonstick and stain resistant coatings of cookware, foods containers, carpets and furniture (Lindstrom et al., 2011). PFCs are persistent in the

* Corresponding authors at: Cancer Center, School of Public Health, West Virginia University, Morgantown, WV 265050-9190, USA

http://dx.doi.org/10.1016/j.envres.2014.08.011

environment, biomagnified along food chains, and bioaccumulated in many species, including humans. The longer chain (≥C6) PFC species tend to have multiyear human half-lives (Lau et al., 2007). Excretion is mediated by organic anion transporters (OATs) and polypeptides, especially for the carboxylate PFC congeners (Yang et al., 2010; Nakagawa et al., 2008), leading to a theory-based hypothesis that GS could interact with human tissue PFC concentrations. The potential for genetic susceptibility to altered PFC persistence in human tissue is potentially important to human health. PFCs have been associated with human health endpoints including pregnancy-induced hypertension (Darrow et al., 2013), elevated serum cholesterol (Steenland et al., 2009; Frisbee et al., 2010), elevated uric acid and hyperuricemia (Geiger et al., 2013), diminished vaccine response (Grandjean et al., 2012), altered thyroid function (Knox et al., 2011; Ji et al., 2012), osteoarthritis (Uhl et al., 2013), and inconsistently with several urogenital cancers (Barry et al., 2013). Studies published to date have not convincingly linked serum bilirubin to PFC exposure in the general population (Costa et al., 2009; Sakr et al., 2007; Emmett et al., 2006; Gallo et al., 2012). However, published studies do not address the subset of the population who manifest GS and who may be susceptible to decreased excretion of xenobiotics, including PFCs. Characterizing any differences in PFC excretion for phenotypic GS, compared to the rest of the population, is the goal of this investigation.

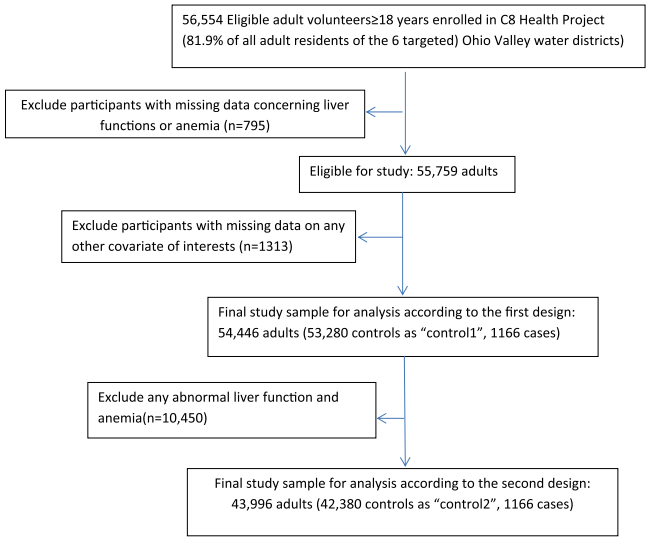

Fig. 1. Selection of the study sample in an investigation regarding the association of PFC levels with risk of Gilbert syndrome phenotype in a large Appalachian population exposed to PFC contaminated drinking water.

2. Study design

2.1. Data sources and study population

The C8 Health Project enrolled participants from August 2005 to August 2006 who had a current or past history of living, working, or going to school in six perfluorooctanoic acid (PFOA)-contaminated water service districts in Ohio and West Virginia. Project details, from enrollment to data collection, cleaning, and reporting, have been published elsewhere (Frisbee et al., 2009). Participation among adult residents of the affected water districts has been estimated at 81.9% (Frisbee et al., 2009). Institutional review board permission was obtained to analyze the de-identified project data.

For this investigation, the study population included those who were age 18 or older with no missing data on serum alanine transaminase (ALT), aspartase amino transferase (AST), lactate dehydrogenase (LDH), direct and total bilirubin hemoglobin, measures of socioeconomic status, alcohol consumption, and cigarette smoking (Fig. 1). GS case inclusion criteria were selected for consistency with the laboratory detection of GS (Fretzayas et al., 2012) including: A) those whose total bilirubin (direct plus indirect) was 1.1–4.9 mg/dl, but direct bilirubin was <0.4 mg/dl; and B) AST <41 IU/L, ALT <41 IU/L, and LDH <333 mg/dl. The absence of elevated levels of these three enzymes (AST, ALT, and LDH) will generally rule out liver disease and causes of elevated indirect bilirubin other than GS. In addition, GS case participants were not anemic (had hemoglobin ≥ 12.1 (females) or ≥ 13.8 (males)), so that anemia and hemolysis were also unlikely to have contributed to a spurious GS classification (Fretzayas et al., 2012).

Exclusion of persons with missing laboratory data (Fig. 1) left a total 55,759 eligible adults. Those who had missing data on socioeconomic status, alcohol consumption, or cigarette smoking or other potential confounding variables ($n=1313$) were also excluded from analyses, for a final study sample of 54,446, including 1166 adults with phenotypic GS, and a comparison population of 53,280 who do not have GS (Control 1). A second, more rigorous comparison, Control 2 ($n=42,380$) excluded 10,450 adults with abnormal liver function tests or anemia from the study comparison population. The associated prevalence rate (2.6%) can be compared to previously reported population prevalence of the phenotypic expression of the syndrome in populations (3–8% in healthy individuals) (Owens and Evans, 1975; Kathemann et al., 2012).

2.2. Blood sample processing and laboratory methods

Blood processing and analytical methods, along with quality-assurance measures, have previously been described (Frisbee et al.,

Table 1
Baseline characteristics of the study population ([ng/ml]/mean ± sd).

Characteristics	Cases $n=1166$	Control 1 $n=53,280$	P-value[a]	Control 2 $n=42,830$	P-value[b]
Age (years)	41.79 ± 17.08	45.37 ± 16.18	<0.0001	45.01 ± 16.14	<0.0001
BMI(kg/m^2)	26.28 ± 5.35	28.65 ± 6.43	<0.0001	28.22 ± 6.31	<0.0001
Gender (female, %)	31.13	52.83	<0.0001	57.07	<0.0001
Race (white, %)	97.08	97.22	0.8600	97.28	0.8090
Educational level (some college or above, %)	50.52	45.54	<0.0001	45.64	<0.0001
Average annual household income (≥30,000, %)	56.95	51.60	<0.0001	51.19	<0.0001
Smoking status (current, %)	11.49	26.54	<0.0001	28.21	<0.0001
Currently drink alcohol (yes, %)	50.51	48.44	0.1605	48.54	0.1828
Regular exercise program (yes, %)	39.37	30.96	<0.0001	31.49	<0.0001

[a] Comparison with Control 1, the probability value of Chi-square for categorical variable, the probability value of t-test for continuous variable.
[b] Comparison with Control 2, the probability value of Chi-square for categorical variable, the probability value of t-test for continuous variable.