CORRELATIONS AMONG SERUM CONCENTRATIONS OF HIGHLY PREVALENT ORGANOCHLORINE COMPOUNDS IN PATIENTS WITH EXOCRINE PANCREATIC CANCER

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Introduction

Organochlorine compounds (OC) represent a large class of chemicals with different characteristics, sources and patterns of exposure and behaviour in the environment, the food chain and human beings. While information on correlations among OC in the environment is available from different geographic areas, the amount of information on this issue in humans is much lower; for exocrine pancreatic cancer (EPC), data are available from just two studies.[1,2] Furthermore, as a result of their physico-chemical properties and metabolism in the human body, correlations between compounds differ from those observed in air, water, soil or food. In Spain barely any studies have reported correlations among internal concentrations of OC in humans.

Exposure to a specific OC may be related with exposure to other OC depending on the source of the OC; for instance, commercial polychlorinated biphenyls (PCBs) were marketed with different proportions of chlorine by weight, and a variety of congeners are usually present in a particular product.[3] Thus, correlations between concentrations of specific compounds can help to determine common sources of exposure. They can also improve understanding of collinearity; this statistical phenomenon may confound risk estimates when assessing the effects of OC upon humans. While knowledge on the causes of EPC is limited, some OC have been implicated as potential causal agents.[1,2,4,5] The aim of this study was to analyse correlations between serum concentrations of the most prevalent OC in patients with EPC.

Subjects and methods

Between 1992 and 1995, all EPC cases newly diagnosed at 5 general hospitals in the mediterranean coast of Spain were prospectively included in the PANKRAS II Study (n=185).[1,4] Over 88% were personally interviewed in-hospital. Serum concentrations of OC were analysed in 144 subjects by high-resolution gas chromatography with electron-capture detection. Calibration lines were calculated and the compounds were then quantified by external standard methods after replicating the analyses.[6] Samples were analysed in two periods. In 1997, serum samples from 51 subjects with EPC were analysed (phase I)[2]; in 2001, analyses included samples from 93 cases (phase II). A conversion factor was obtained by linear regression of samples with quantified values and, in order to equalise values from the two periods, it was applied to samples from phase I. In phase I limits of detection and quantification (ng/mL) were: 0.09 and 0.3 for p,p'DDT, 0.6 and 2 for p,p'DDE, 0.1 and 0.33 for PCB 138, 0.24 and 0.79 for PCB 153, 0.4 and 1.3 for PCB 180, 0.23 and 0.76 for hexachlorobenzene (HCB) and 0.6 and 2.1 for b-hexachlorocyclohe-xane (b-HCH). In phase II, they were 0.26 and 0.39 for p,p'DDT, 0.09 and 0.14 for p,p'DDE, 0.11 and 0.16 for PCB 138, 0.12 and 0.18 for PCB 153, 0.10 and 0.16 for PCB 180, 0.03 and 0.05 for HCB, and 0.15 and 0.22

for b-HCH. When a sample had an OC concentration below the detection threshold, it was assigned the mid-value of this limit; when an OC was detected but under the quantification threshold, the mid-value between detection and quantification limits was assigned. In statistical analyses, Spearman's rank correlation coefficient (r) was used to evaluate correlations between compounds. A cluster analysis was performed to classify the compounds into similar groups. Different linkage methods were used to determine the similarity / distance between two clusters; results were similar with all linkage methods. We present results using Pearson's correlation coefficient (as the distance measure), and the average linkage method (where the distance between two clusters is defined as the average distance between a variable in one cluster and a variable in the other cluster).

Results and discussion

Concentrations (median, ng/mL) for the seven OC were as follows: p,p'DDT and p,p'DDE 2.92 and 19.49; PCBs 138, 153 and 180: 1.55, 1.68 and 1.66; HCB: 10.31; and b-HCH: 6.26.

In this study p,p'DDT and p,p'DDE were moderately correlated. As shown in table 1, in the 144 cases of EPC the r between them was 0.576. The fact that concentrations of the two compounds are not independent bears important implications for studies aiming at elucidating the specific ethiopathogenic role of each OC. The correlation between DDT and DDE was stronger in cases older than 60 years ($r = 0.603$, $p<0.001$) than in younger cases ($r = 0.476$ $p = 0.001$). This suggests that younger subjects incorporated the two compounds in a more independent way than older subjects; hence, while in the elderly a larger proportion of the p,p'DDE body burden would stem from metabolization of p,p'DDT, the predominant source of DDE in younger cases would be background dietary exposure.

Correlations tended to be higher between compounds with higher serum concentrations, such as the two PCBs with highest concentrations, congeners 138 and 153. Spearman's coefficients and their degree of statistical significance are also shown in table 1 for the 3 pairs of more predominant congeners (138, 153 and 180). Such correlations were somewhat weaker in older than in younger cases; among the latter, they ranged from 0.794 for congeners 138 and 180, to 0.922 for congeners 138 and 153. Correlations between pairs of compounds were similar in women and men. All coefficients were higher than 0.642, which was the correlation between congeners 138 and 180 in men. These findings are in accordance with previous reports.

The r between HCB and b-HCH was also high ($r = 0.758$, $p<0.001$). It was similar in men ($r = 0.763$, $p<0.001$) and in women ($r = 0.705$, $p<0.001$), as well as in older ($r = 0.718$, $p<0.001$) and younger cases ($r = 0.746$, $p<0.001$). Although one reason for the association between HCB and b-HCH may lie in their similar properties, and similar behaviour in humans, a comprehensive explanation is at present lacking.

All other correlations were below 0.5 (table 1). The highest correlations involved b-HCH: almost all were between 0.4 and 0.5. Correlations with b-HCH were similar in women and men, and among older and younger subjects. In younger cases, we also observed moderate correlations between PCB 138 and p,p'DDT ($r = 0.511$, $p<0.001$), PCB 138 and p,p'DDE ($r = 0.460$, $p = 0.002$), PCB 153 and p,p'DDT ($r = 0.446$, $p = 0.002$), and between PCB 153 and p,p'DDE ($r = 0.411$, $p=0.006$).

Multivariate clustering analysis may help to identify possible common sources and pathways of exposure for different OC. The procedure seeks to organise information about variables so that relatively homogeneous groups, or clusters, can be formed. This agglomerative hierarchical method begins analysis with all variables separate, each forming its own cluster. In the first step, the two closest variables are joined together. In the next step, either a third variable joins the first two, or two other variables join together into a different cluster. Whilst the process continues until all clusters are joined into one, it is necessary to decide how many groups are logical for the data analysed.

Table 1. Correlations among organochlorine compounds among 144 subjects with exocrine pancreatic cancer (PANKRAS II Study). Spearman's rank correlation coefficient (and p value)

	p,p'DDT	p,p'DDE	PCB 138	PCB 153	PCB 180	HCB
p,p'DDE	0.576 (<0.001)					
PCB 138	0.297 (<0.001)	0.341 (<0.001)				
PCB 153	0.270 (0.001)	0.350 (<0.001)	0.840 (<0.001)			
PCB 180	0.248 (0.003)	0.212 (0.011)	0.660 (<0.001)	0.811 (<0.001)		
HCB	0.302 (<0.001)	0.284 (0.001)	0.259 (0.002)	0.288 (<0.001)	0.129 (0.125)	
b-HCH	0.428 (<0.001)	0.485 (<0.001)	0.405 (<0.001)	0.447 (<0.001)	0.259 (0.002)	0.758 (<0.001)

The similarity (s) between two clusters i and j (s_{ij}) is given by $s_{ij} = 100 * (1- d_{ij} / d_{max})$. In our case, $d_{max} = 2$ because correlation (d_{ij}) was chosen as the distance measure; s_{ij} ranges from 100, when the correlation is equal to 1, to 50 when the correlation is equal to 0.

As shown in figure 1, the two first compounds that are joined together are PCBs 138 and 153 (s = 93.23). The compound closest to them is congener 180 (similarity, 85.30); the next cluster forms between p,p'DDT and p,p'DDE (s = 78.01); and the third cluster between HCB and b-HCH (s = 74.86). These results are consistent with results from correlation analysis.

Correlations among OC need to be assessed when interpreting etiologic studies in humans. If the fact that two chemicals are correlated but just one is causally related to the outcome is ignored, then the effect of the causally related compound may be underestimated; or, worse, an spurious relation between the unrelated compound and the outcome may be apparent.[7] A moderate or high correlation between the concentrations of two OC is an additional reason to assess whether they jointly have additive, multiplicative or antagonistic effects. Therefore, the actual magnitude of associations between specific OC and outcomes may be under- or overestimated unless correlations among OC are taken into account. Knowledge on the physico-chemical properties of the compound is essential to guide the statistical analyses. Empirical evidence and sound hypotheses on the biological or epidemiological relation between the compound and the biological or clinical outcomes of interest are equally important.

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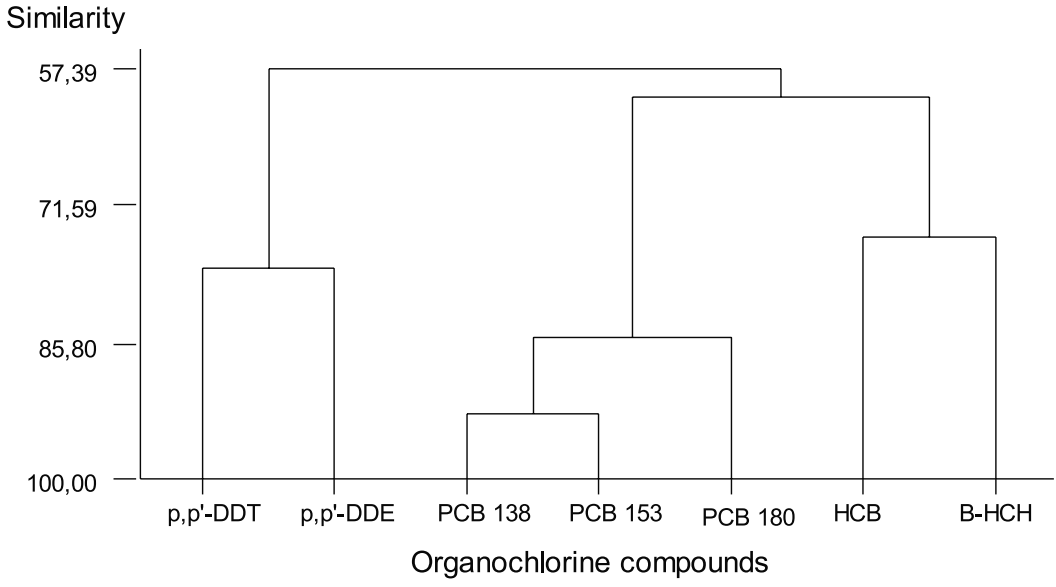

Figure 1. Dendogram of the clustering analysis for the seven organochlorine compounds

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