PHYSIOLOGICAL BASED MODELLING OF THE ELIMINATION OF POLYCHLORINATED DIBENZOFURANS (PCDFS) IN HUMANS IN THE RICE OIL POISONINGS

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The rate and selectivity of the elimination of the persistent and toxic congeners of the PCDFs and PCBs from the bodies of both yusho and yu-cheng individuals is important not only for the health of the victims but also with respect to interpretation of the kinetics and disposition of lower doses found in general populations. Previous work by us using blood specimens had shown that levels of PCDFs and possibly PCBs decreased in a non-linear fashion[1,2,3]. Faster clearance occurred at higher dose followed by slower losses as so-called background or normal concentrations were attained. However the explanation or rationalization of these non-linear kinetics, although known from other xenobiotics such as 2,3,7,8-TCDD in rats[4] and PCBs in capacitor workers[5], is not readily evident.

Physiologically based pharmacokinetic (PBP) models using known and derived biological constants along with their mathematical relationships have been increasingly used to interpret the distribution and clearance of a number of compounds. One of us (GC) has recently developed a PBP model for dioxin-like compounds in both experimental animals and man[6,7,8]. We have now applied this model to the elimination of PCDFs and PCBs from human blood using the recent values from both the yusho and yu-cheng patients[3]. In addition, we use the model to predict the blood values which we anticipate to find in blood samples collected recently from these same individuals.

METHODS

The distinctive features of the model are the following:

1) The total body burden or body concentration of dioxin-like compounds (those chlorinated aromatic hydrocarbons which bind to the Ah receptor) in both animals and man at any one time resides almost entirely in the liver and adipose tissue compartments. Other tissues are of little or no consequence.

2) The absorption and distribution of PCDDs/PCDFs/pPCBs in the human body is much faster (order of hours to days) than their elimination (order of months to years) such that near equilibrium is reached before body burdens change substantially.

3) Due to the capacity of specific liver proteins to bind circulating ligands, the fraction in the liver (f_h) is the bioindicator of adverse effect. The functional dependency of f_h and the fraction in the adipose tissue (f_{at}) on the overall body concentration (C_b) is determined using a modified Michaelis-Menten equation with the result that C_b and the concentrations in the liver (C_h), and

adipose (C_{at}) vary nonlinearly. C_b and f_h increase with a corresponding decrease in f_{at}. The important parameter f_h varies from less than 0.01 for lowly exposed individuals to a maximum of more than 0.6 in severely exposed yusho and yu-cheng cases exhibiting overt toxicity.

4) The body burden is eliminated at a rate that is proportional to the fraction present in the liver. A mass balance differential equation using anatomically and physiologically relevant parameters (body weight, liver and adipose tissue amounts and age) is solved to predict the fate of PCDDs/PCDFs in liver, adipose tissue and whole body as a function of time. The rate of change of tissue concentrations decreases as body burden decreases. Concomitant with this elimination, tissue half-lives lengthen.

5) The model estimates many of its own parameters such as f_{hmax}, the dissociation constant K, and the elimination rate constant. This allows predictions of parameters such as adipose tissue concentrations, total body burden, partitioning among tissue compartments, and half-lives.

RESULTS

One of the individuals (BS) from our earlier work[3] is used to illustrate the model. This person was aged 17 and weighed 59 kg in 1989 and his liver and adipose tissue weight relative to total body weight over the entire period was estimated to be 0.03 and 0.2, respectively. Using these data and the C_{at} for the toxicologically important 2,3,4,7,8-PnCDF congener derived from blood levels over 10 years, the following parameters were obtained: $f_{hmin}=0.009$, $f_{hmax}=0.717$, and K=476 ng 2,3,4,7,8-PnCDF/kg body weight. Comparison of the measured blood data (equivalent to C_{at}) and that predicted from the model shows good agreement except for the initial period. This latter discrepancy may be due to effects of tissue distribution or weight changes associated with high initial exposure.

The Table shows simulated tissue concentrations and half-lives over a period of 50 years following poisoning in this same individual. Half-lives are not constant but vary as a function of tissue concentrations from 1 up to 30 years. The lower the concentration, the longer the half-life. The half-lives for C_b and C_{at} change more than those for C_h. Graphically, the concentrations show a steep change for the first 10 to 12 years followed by a plateau effect thereafter. Initially, the concentrations in the liver are higher than those in adipose tissue and, after about 10 years, the reverse is true. For even lower exposure such as those of normal populations, liver concentrations are significantly lower than adipose tissue concentrations. The kinetic profile for humans is similar to other mammals such as rats and monkeys; however, the duration for humans is considerably longer. From the table we predict for the individual BS that i) his C_{at} from blood sampled in 1993 will be less than 400 ng/kg lipid and ii) that he will never attain background levels (less than about 30 ng/kg) in his lifetime. We are currently analyzing these yu-cheng blood samples to test the validity of the model further.

Table. Simulation of relationship between tissue concentrations and half-lives of 2,3,4,7,8-PnCDF in a Yu-Cheng patient (BS) for 50 years post-poisoning. The concentration of blood lipids (C_{at}) at t = 0 was 15300 ng PnCDF/kg lipid. (from data by Ryan et al., 1993)

Time	Concentrations (ng PnCDF/kg)			Half-life (years)		
(Years)	$C_b(t)$	$C_h(t)$	$C_{at}(t)$	$t½C_b(t)$	$t½C_h(t)$	$t½C_{at}(t)$
0	10409.61	238047.39	15300.00	0.97	0.92	1.14
2	2611.46	52912.11	4859.32	1.16	0.96	1.69
4	837.09	12845.00	2174.97	1.66	1.12	2.52
6	369.94	3929.00	1223.36	2.59	1.49	3.53
8	209.69	1576.30	791.05	3.82	2.01	4.75
10	138.82	781.33	563.00	5.21	2.62	6.12
12	101.13	448.52	428.24	6.69	3.29	7.57
16	63.41	194.93	281.46	9.70	4.73	10.53
20	45.14	105.81	205.31	12.67	6.24	13.45
24	34.55	65.56	159.48	15.53	7.78	16.27
28	27.71	44.28	129.13	18.27	9.34	18.96
30	25.13	37.28	117.54	19.60	10.13	20.26
32	22.94	31.78	107.65	22.88	10.91	21.53
36	19.45	23.85	91.71	23.36	12.48	23.97
40	16.78	18.51	79.43	25.70	14.05	26.28
44	14.68	14.77	69.71	27.93	15.61	28.47
48	12.99	12.03	61.82	30.04	17.16	30.55
50	12.26	10.94	58.42	31.05	17.93	31.55

CONCLUSION

A physiological based pharmacokinetic model has been developed using data from the rice oil incidents to explain the elimination of PCDDs/PCDFs from humans. The salient features are the fractionation of the dose between liver and adipose tissue and the non-linearity of the clearance. Application and stimulation of the model with measured blood values from yu-cheng allows prediction of the long term course of loss from the body.

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