PROMOTIVE EXCRETION OF POLYCHLORINATED DIBENZOFURANS BY FBRA IN PATIENTS WITH YUSHO

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Introduction

Polychlorinated dibenzofurans (PCDFs) have been the most important etiological agents of Yusho [1) 2)], a mass food poisoning that occurred in western Japan in 1968. At present, namely, 40 years after the outbreak, many patients with Yusho are still suffering from several objective and subjective symptoms.

In order to improve or to cure various symptoms of patients with Yusho, the promotive excretion of causative PCDFs congeners from the body of the patients is considered very useful. In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion of dioxins, probably due to the restriction or some inhibition of their absorption and re-absorption in the digestive tract and therefore to reduce their levels in rat liver [3) 4)]. In this study, we examined whether such kinds of effect were observed by the intake of FBRA, which was the brown rice fermented with *Aspergillus-oryze* and rich with dietary fiber, or not in patients with Yusho.

Materials and Methods

FBRA has been manufactured for almost 40 years with Genmaikouso Corp., Sapporo, Japan, and taken by more than 100,000 people as one of the health foods. Ingredients of FBRA have already been reported in our previous study [5)].

Eighteen patients with Yusho were voluntarily participated in this study, and divided into two groups in compliance with their wishes, namely, groups A and B. Group A consisted of 3 males and 7 females with the mean age of 67.7 years old and group B 4 males and 4 females with that of 64.1 years old. In group A, they took 7.0 to 10.5g of FBRA after each meal and three times a day for the first one year and didn't for the second one year. In group B, they took FBRA in the same way as group A in the second one year, but not in the first one year.

Just before starting this study, 20 ml of the peripheral blood was individually taken by venipuncture in both groups A and B, twice at one week intervals. These blood samples were analyzed for PCDFs including 2,3,4,7,8-pentachloro-dibenzofuran (2,3,4,7,8-PenCDF), 1,2,3,4,7,8-hexachlorodibenzofuran (1,2,3,4,7,8-HxCDF) and 1,2,3,6,7,8-HxCDF, which were the most important causative PCDFs congeners for Yusho disease, by HRGC-HRMS technique using a Micromass Autospec Ultima NT mass spectrometer directly interfaced with an Agilent Technologies HP-6890A gas chromatography [6)]. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) toxic equivalent (TEQ) concentration of PCDFs were calculated by using 1998 WHO TCDD toxic equivalency factor values [7)]. The average concentrations of PCDFs and the three PCDF congeners in the two blood samples of the same patient were expressed as the individual original ones in both groups A and B. In order to evaluate the effect of FBRA on their excretion from the patients, their blood concentrations were determined again exactly with the same manner as those measured just before beginning this study at the end of first and second year in both groups. Their concentrations measured at different times in each group were statistically examined by student's t-test.

Results and Discussion

Changes in concentrations on whole weight basis of PCDFs and the three PCDF congeners in the blood of patients with Yusho during the period of this study were shown in Table 1. Just before starting this study, concentrations of PCDFs, 2,3,4,7,8-PenCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF in group A were 0.747 ± 0.952 pg-TEQ/g, 1.36 ± 1.71, 0.491± 0.734 and 0.150 ± 0.195 pg/g, respectively, and those in group B 0.310 ± 0.248 pg-TEQ/g, 0.571 ± 0.465, 0.159± 0.113 and 0.064 ± 0.037 pg/g. Although their concentrations were 2.3 to 3.1 times higher in group A than in group B, even in group B these were 3 to 11 times greater than those in healthy Japanese people, and the concentrations of 2,3,4,7,8-PenCDF, the main causative PCDFs congener of Yusho, were the highest and 11 times over those of healthy people [8]. These results clearly indicate that patients with Yusho are still contaminated with high levels of PCDFs and in order to improve their objective and subjective symptoms, promotive excretion of PCDFs seems quite important.

As indicated in Table 1, mean concentrations of PCDFs, 2,3,4,7,8-PenCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF gradually decreased from the beginning to the end of this study, except those of 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs in group A, in which their concentrations increased from the end of first year to the end of second year and in this period they did not take FBRA.

Table 1. Changes in concentrations on whole weight basis of PCDFs and three PCDFs congeners in the blood of patients with Yusho

	Concentration, pg/g whole weight*		
Congener	Initial	After 1st year	After 2nd year
2,3,4,7,8-PenCDF			
Group / A	1.36 ± 1.71	1.32 ± 1.68	1.31 ± 1.67
B	0.571 ± 0.465	0.570 ± 0.476	0.561 ± 0.473
1,2,3,4,7,8-HxCDF			
Group / A	0.491 ± 0.734	0.410 ± 0.609 [a]	0.423 ± 0.648 [a]
B	0.159 ± 0.113	0.148 ± 0.107	0.144 ± 0.113
1,2,3,6,7,8-HxCDF			
Group / A	0.150 ± 0.195	0.128 ± 0.159 [a]	0.133 ± 0.174 [a]
B	0.064 ± 0.037	0.061 ± 0.037	0.060 ± 0.040
PCDFs			
Group / A	0.747 ± 0.952	0.720 ± 0.921 [a]	0.712 ± 0.919 [a]
B	0.310 ± 0.248	0.308 ± 0.253	0.303 ± 0.253 [b]

* : Mean ± S.D.

** : pg-TEQ/g whole weight

[a] : Significantly different from the initial concentration in group A, $p<0.05$

[b] : Significantly different from the initial concentration in group B, $p<0.05$

We have already mentioned that quantitative and reproducible lipid extraction from the blood and breast milk is very difficult [9) 10)] and at present, we should use the concentrations on whole weight basis instead of on lipid weight basis to get much precise concentrations of PCDFs and so forth. Therefore, in order to convert the mean concentrations in Table 1 to those on lipid weight basis, we presumed the lipid content of blood was 0.3%, and the results are shown in Table 2. Again, on the assumption that the body fat was contaminated with PCDFs and the three PCDF congeners at their blood concentrations on lipid weight basis and the content of body fat was 20% of body weight (60kg), we calculated their total body burdens and evaluated the effects of the intake of FBRA for one year on the excretion of PCDFs and the three PCDF congeners from the body of patients with Yusho in groups A and B.

Net reduction of 2,3,4,7,8-PenCDF in the body of patients with Yusho were 120 and 36 ng/ patient in groups A and B, respectively, as shown in Fig. 1. Net reduction of 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs were 372 and 96 ng/ patient, respectively, only in group A. We, however, could not find any significant reduction of these two HxCDFs congeners in group B, as also indicated in Fig. 1, net reduction of PCDFs were 72 and 24 ng-TEQ/patient in groups A and B, respectively.

We have already reported the promotive excretion of PCDFs and PCDDs from healthy Japanese people by one year intake of FBRA [5, 11, 12)]. Results of this study also confirmed the promotive excretion of PCDFs from the patients with Yusho by the intake of FBRA, and showed that this reduction seemed more effective in the patients with higher concentrations of PCDFs, namely, in group A.

Table 2. Changes in mean concentrations on lipid weight basis of PCDFs and three PCDF congeners in the blood of patients with Yusho

	Mean Concentration, pg/g lipid weight*		
Congener	Initial	After 1st year	After 2nd year
2,3,4,7,8-PenCDF			
Group / A	453	440	437
B	190	190	187
1,2,3,4,7,8-HxCDF			
Group / A	164	137	141
B	53	49	48
1,2,3,6,7,8-HxCDF			
Group / A	50	43	44
B	21	20	20
PCDFs**			
Group / A	249	240	237
B	103	103	101

* : Lipid content of the blood was supposed 0.3%
** : pg-TEQ/g lipid weight

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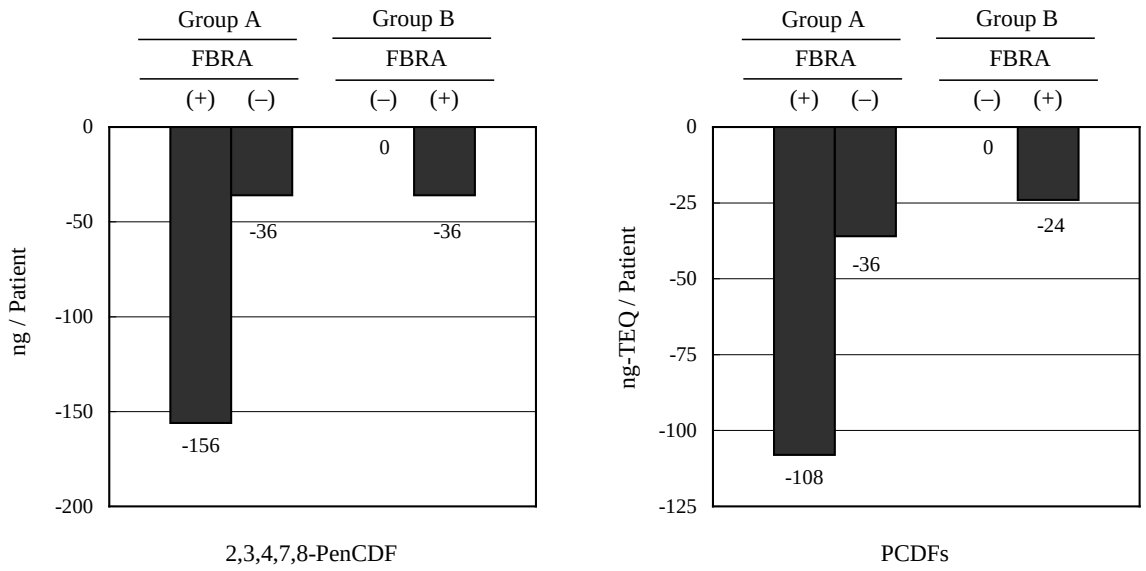

Fig. 1. Effects of the intake of FBRA for one year on the excretion of 2,3,4,7,8,-PenCDF (left) and PCDFs (right) from the body of patients with Yusho