Effect of colestimide on the concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dizenzofurans, and polychlorinated biphenyls in blood of Yusho patients

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Abstract

Background: Oral colestimide was reported to lower the concentration of PCDDs, PCDFs, and PCB in the blood of humans. A pilot study showed that the arithmetic mean total TEQ concentrations of PCDDs, PCDFs, and PCBs in the blood of subjects after the trial decreased approximately 20 % compared to pre-trial levels, suggesting that colestimide could decrease human dioxin levels. We designed the current clinical trial study based on this information. In this study, we examined whether colestimide could reduce the individual congener concentrations of PCDDs, PCDFs, and PCBs in the blood of Yusho patients.

Methods: Out of the 36 Yusho patients who participated in the clinical trial, 26 patients self-administered colestimide 3 g/day orally for 6 months. The concentrations of PCDDs, PCDFs and PCBs in the blood of 26 Yusho patients before the trial were compared with those after the trial.

Results: The arithmetic mean total TEQ concentrations of PCDDs, PCDFs, non-ortho PCBs, and mono-ortho PCBs in the blood of the 26 Yusho patients before and after the clinical trial were 42–303 (mean: 130, median: 120) and 43–283 (mean: 132, median: 118) pg TEQ/g lipid, respectively. The sums of the concentrations of 58 PCB congeners measured in the blood of Yusho patients before and after the trial were 321–2643 (mean: 957, median: 872) and 286–2007 (mean: 975, median: 806) ng/g lipid, respectively, indicating that the concentrations of PCDDs, PCDFs, and PCBs after the trial were almost the same as those before the trial. Among congeners of PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs, most congeners of these compounds did not show a statistically significant decrease after the trial.

Conclusion: Colestimide may not be beneficial in reducing the high blood levels of dioxin-like compounds in Yusho patients.

Keywords: PCDDs, PCDFs, PCBs, Yusho, Colestimide, Blood concentration

Background

The 1968 Yusho poisoning accident affected over 1800 people in western Japan [1]. Since the Yusho outbreak, the National Study Group for the Therapy of Yusho has carried out medical care and health examinations of patients affected [2]. In 2001, the measurement of PCDDs, PCDFs, and non-ortho PCBs in the blood became possible using small amounts of blood collected from participants during annual medical examinations [3–5]. We have measured the concentrations of PCDDs, PCDFs, and dioxin-like PCBs in the blood collected from Yusho patients in medical health examinations since 2002 [6–8]. Moreover, we have conducted a congener-specific analysis of non-dioxin-like PCBs in the blood of these patients since 2004 [9, 10].
Based on these results, we previously reported that Yusho patients continue to have higher concentrations of PCDFs in their blood than unaffected people, and that concentration of PCDFs in the blood is significantly correlated with the intensity of Yusho symptoms [11, 12]. Development of effective therapy to reduce the concentrations of PCDDs, PCDFs, and PCBs in the blood of Yusho patients could improve the health care of these patients. With regard to promoting the excretion of lipophilic contaminants stored in the human body, several studies of dietary supplements such as cholestyramine, mineral oil, hexadecane, and dietary fiber have been reported using laboratory animals [13–16]. In addition, another study reported the enhancing effect of non-absorbable lipid substitute olestra on fecal excretion of PCDDs, PCDFs, and PCBs in the human body [17, 18]. Our study group previously conducted a clinical trial to reduce the concentrations of PCDDs, PCDFs, and PCB in the blood of Yusho patients using cholestyramine and rice bran fiber [19, 20]. However, beneficial clinical effects could not be confirmed due to the short trial period.

Colestimide, a 2-methylimidazobenzepin polymer, is widely used to lower serum cholesterol levels in Japan. Recently, oral colestimide was reported to lower the concentration of PCDDs, PCDFs, and PCB in the blood of humans [21, 22]. A pilot study showed that the arithmetic mean total TEQ concentrations of PCDDs, PCDFs, and PCBs in the blood of subjects after the trial decreased approximately 20 % compared to pre-trial levels, suggesting that colestimide could decrease human dioxin levels [21, 22]. We designed the current clinical trial study based on this information. In this study, we examined whether colestimide could reduce the individual congener concentrations of PCDDs, PCDFs, and PCBs in the blood of Yusho patients.

**Methods**

**Sampling**

The trial protocol was approved by the institutional ethics committee of Kyusyu University Hospital. Patients who fulfilled the diagnostic criteria for Yusho established by the National Study Group for the Therapy of Yusho were eligible for this study. Patients were recruited at explanatory meetings conducted in Fukuoka and Nagasaki Prefectures. 50 Yusho patients were enrolled in this clinical trial, and 14 patients refused to participate. The remaining 36 patients participated in the trial. Informed consent was obtained for study participation. The patients self-administered colestimide 3 g/day orally for 6 months. Out of the 36 Yusho patients who participated in the clinical trial, 26 patients completed the trial. The 26 patients ranged in age from 60 to 87 years (mean: 72.9, median: 72.5). Among the 26 patients, there were 13 men (age range 60–87 years; mean: 73.1, median: 74.0) and 13 women (age range 61–81 years; mean: 72.8, median: 72.0). The blood samples examined in this study were collected between April 4, 2008 and July 15, 2009. After collection, the blood samples were stored at 4 °C until analyses.

**Materials**

Native congeners of PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs were purchased from Wellington Laboratories (Guelph, Canada). \[^{13}C_{12}\]–congeners of PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs as internal standards, were also purchased from Wellington Laboratories. An active carbon column was prepared as follows: active carbon was purchased from Nacalai Tesque (Kyoto, Japan), refluxed 3 times with toluene for 1 h, and dried in vacuum, after which 500 mg of the active carbon was mixed with 500 g of anhydrous sodium sulfate (Wako Pure Chemical Industries, Ltd., Tokyo, Japan). A silver nitrate/silica gel was purchased from Wako Pure Chemical Industries, Ltd. All reagents and solvents used in this experiment were of the analytic grade of dioxin that is commercially available.

**Analysis of PCDDs, PCDFs, and PCBs**

The extraction and purification of PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs from blood samples were performed using a previously reported method [5, 9]. Concentrations of PCDDs, PCDFs, and dioxin-like PCBs and concentrations of 58 non-dioxin-like PCB congeners were determined by a previously reported method [5, 9].

**Quality control**

To evaluate the accuracy and reliability of the analysis of PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs, our laboratory prepared human blood samples and conducted quality control studies of the analysis of PCDDs, PCDFs, and dioxin-like PCBs in 2007, 2009, 2011, and 2013 and non-dioxin-like PCBs in 2008, 2010, 2012, and 2014. Each quality control study involved the participation of various laboratories that perform measurements for these compounds in human blood in Japan. In each quality control study, our results were compared with those of participating laboratories, and tests confirmed that the average variation among values obtained by each organization performing the analysis was all within 10 %. These results indicated that our laboratory's analytical methods regarding PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs in human blood provided accurate results.
| Congeners | Concentration (pg/g lipid) | Before the clinical trial | After the clinical trial | p Values |
|-----------|---------------------------|--------------------------|--------------------------|----------|
|           |                           | Mean | Median | SD | Minimum | Maximum | Mean | Median | SD | Minimum | Maximum |
| 2,3,7,8-TetraCDD | 1.8 | 1.7 | 0.9 | 0.5 | 4.0 | 2.0 | 1.8 | 1.2 | 0.5 | 4.7 | 0.083 |
| 1,2,3,7,8-PentaCDD | 14 | 14 | 4.9 | 6.6 | 23 | 14 | 12 | 6.1 | 6.1 | 27 | 0.067 |
| 1,2,3,4,7,8-HexaCDD | 3.1 | 3.0 | 1.7 | 1.0 | 7.1 | 3.3 | 3.2 | 1.7 | 1.0 | 6.9 | 0.053 |
| 1,2,3,6,7,8-HexaCDD | 62 | 53 | 36 | 16 | 183 | 63 | 55 | 34 | 15 | 164 | 0.258 |
| 1,2,3,7,8,9-HexaCDD | 5.5 | 4.5 | 5.2 | 2.1 | 29 | 5.7 | 3.9 | 6.0 | 1.0 | 31 | 0.770 |
| 1,2,3,4,6,7,8-HeptaCDD | 55 | 47 | 25 | 21 | 113 | 52 | 43 | 27 | 20 | 143 | 0.137 |
| OctaCDD | 699 | 606 | 281 | 323 | 326 | 670 | 543 | 309 | 305 | 1610 | 0.118 |
| Total PCDD | 841 | 739 | 315 | 413 | 1525 | 811 | 688 | 346 | 382 | 1850 | 0.144 |
| 2,3,7,8-TetraCDF | 2.8 | 2.7 | 1.3 | 0.5 | 5.5 | 2.7 | 2.6 | 1.4 | 0.5 | 5.8 | 0.427 |
| 1,2,3,7,8-PentaCDF | 1.3 | 1.1 | 0.9 | 0.5 | 3.5 | 1.5 | 1.2 | 1.1 | 0.5 | 4.4 | 0.554 |
| 2,3,4,7,8-PentaCDF | 241 | 191 | 158 | 48 | 636 | 242 | 205 | 158 | 49 | 613 | 0.732 |
| 1,2,3,4,6,7,8-HexaCDF | 64 | 51 | 56 | 7.8 | 227 | 64 | 52 | 56 | 8.1 | 207 | 0.990 |
| 1,2,3,7,8,9-HexaCDF | 26 | 21 | 19 | 6.2 | 86 | 26 | 22 | 19 | 5.2 | 74 | 0.534 |
| 1,2,3,7,8,9,9-HexaCDF | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| OctaCDF | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Total PCDF | 342 | 280 | 229 | 71 | 963 | 344 | 292 | 230 | 71 | 890 | 0.732 |
| 33’4’4’-TriCB(#77) | 6.9 | 5.0 | 3.7 | 5.0 | 16 | 8.9 | 7.5 | 4.3 | 5.0 | 20 | 0.016 |
| 344’5-TriCB(#81) | 5.3 | 5.0 | 1.4 | 5.0 | 12 | 5.7 | 5.0 | 2.4 | 5.0 | 15 | 0.180 |
| 33’44’5-PentaCB(#126) | 129 | 100 | 81 | 30 | 391 | 131 | 96 | 85 | 34 | 356 | 0.770 |
| 33’44’55’-HexaCB(169) | 279 | 250 | 144 | 104 | 678 | 293 | 280 | 129 | 114 | 585 | 0.101 |
| Total Non-ortho PCBs | 420 | 382 | 178 | 183 | 906 | 439 | 406 | 166 | 196 | 789 | 0.078 |
| 233’44‘-PentaCB(#105) | 4454 | 3145 | 3555 | 1206 | 13788 | 51038 | 30741 | 43667 | 9528 | 180163 | 0.517 |
| 2344‘5-PentaCB(#114) | 2800 | 2365 | 1688 | 5.0 | 7194 | 2997 | 2681 | 1699 | 5.0 | 6987 | 0.118 |
| 2344‘5-PentaCB(#118) | 21718 | 16568 | 17601 | 5.0 | 75475 | 21050 | 15412 | 14335 | 4575 | 57260 | 0.990 |
| 2344‘5-PentaCB(#123) | 304 | 228 | 273 | 5.0 | 1239 | 312 | 214 | 237 | 5.0 | 898 | 0.581 |
| 2334‘5-PentaCB(#156) | 50472 | 32661 | 46375 | 13079 | 195017 | 51038 | 30741 | 43667 | 9528 | 180163 | 0.517 |
| 2334‘5-PentaCB(#157) | 13157 | 8088 | 13150 | 3390 | 53954 | 12747 | 7644 | 11520 | 2332 | 46994 | 0.990 |
| 2344‘5-PentaCB(#167) | 4834 | 4243 | 3373 | 5.0 | 16863 | 4610 | 4265 | 2422 | 985 | 10481 | 0.770 |
| 2344‘5-PentaCB(#189) | 7385 | 5100 | 5888 | 1664 | 24429 | 7398 | 5397 | 5323 | 1730 | 22434 | 0.829 |
| Total Mono-ortho PCBs | 105125 | 83472 | 66740 | 40066 | 293077 | 104734 | 93659 | 59308 | 34746 | 267273 | 0.829 |
| TEQ from PCDDs | 24 | 24 | 7.9 | 11 | 43 | 24 | 24 | 9.2 | 11 | 42 | 0.809 |
| TEQ from PCDFs | 82 | 63 | 54 | 16 | 223 | 82 | 68 | 54 | 16 | 211 | 0.534 |
| TEQ from non-ortho PCBs | 106 | 83 | 60 | 27 | 265 | 107 | 87 | 61 | 28 | 249 | 0.790 |
| TEQ from mono-ortho PCBs | 21 | 20 | 9.8 | 7.4 | 54 | 22 | 20 | 9.7 | 7.8 | 47 | 0.485 |
| TEQ from dioxin-like PCBs | 3.2 | 2.5 | 2.0 | 1.2 | 8.8 | 3.1 | 2.8 | 1.8 | 1.0 | 8.0 | 0.829 |
| Total TEQ | 130 | 120 | 65 | 42 | 303 | 132 | 117 | 65 | 43 | 283 | 0.869 |

ND (less than the detection limit) values introduced to half values of the detection limit and calculated the TEQ concentrations
SD standard deviation, CDD chlorinated dibenzo-p-dioxin, CDF chlorinated dibenzofuran
Table 2 Effect of colestimide on the individual congener concentrations of non-dioxin-like PCBs in the blood of Yusho patients

| IUPAC#          | Concentration (pg/g lipid) | Before the clinical trial | After the clinical trial | p Values |
|-----------------|----------------------------|---------------------------|--------------------------|----------|
|                 | Mean Median SD Minimum Maximum |                          | Mean Median SD Minimum Maximum |          |
| TriCB-28        | 1644 1449 866 324 3809 | 1837 1866 1226 5 6187 | 0.025                   |
| TriCB-29        | 20 12 18 5 72 | 20 5 23 5 99 | 0.845                   |
| TriCB-37        | 128 5 245 5 847 | 73 5 165 5 698 | 0.112                   |
| TeteraCB-44     | 348 248 523 5 2841 | 415 324 415 107 2261 | 0.034                   |
| TeteraCB-47/48  | 525 359 437 117 1769 | 640 471 715 121 3659 | 0.049                   |
| TeteraCB-49     | 295 179 409 44 1679 | 344 216 576 5 3070 | 0.101                   |
| TeteraCB-52/69  | 956 780 836 294 4572 | 1060 860 745 368 3896 | 0.052                   |
| TeteraCB-56/60  | 442 306 344 5 1412 | 489 284 577 104 3010 | 0.089                   |
| TeteraCB-63     | 116 117 65 5 280 | 140 118 69 5 360 | 0.382                   |
| TeteraCB-66     | 2118 1520 1507 586 5853 | 2181 1536 1691 613 8475 | 0.551                   |
| TeteraCB-70     | 362 130 807 13 3375 | 418 143 1308 55 6817 | 0.280                   |
| TeteraCB-71     | 37 11 56 5 238 | 126 5 490 5 2524 | 0.586                   |
| TeteraCB-74     | 14823 12720 9202 3830 41089 | 14505 11875 9068 2973 35194 | 0.770                   |
| PentaCB-85      | 247 139 335 5 1592 | 205 138 218 5 1086 | 0.657                   |
| PentaCB-87      | 812 797 448 5 1716 | 747 697 442 5 2059 | 0.183                   |
| PentaCB-92      | 719 571 482 5 2402 | 752 669 455 5 2264 | 0.412                   |
| PentaCB-93/95/98| 727 637 439 5 1964 | 1003 746 1165 326 6428 | 0.258                   |
| PentaCB-99      | 23623 19114 17453 4240 90085 | 24873 23328 16634 4308 82151 | 0.182                   |
| PentaCB-101     | 1931 1534 1234 5 5667 | 2337 1959 1481 600 6915 | 0.174                   |
| PentaCB-107/108 | 963 785 707 5 3340 | 961 819 584 5 2435 | 0.166                   |
| PentaCB-110     | 339 242 325 5 1451 | 332 298 268 5 1428 | 0.638                   |
| PentaCB-117     | 1911 1466 1813 435 7951 | 1722 1306 1642 5 6579 | 0.280                   |
| HexaCB-128      | 925 685 660 5 3099 | 949 678 775 5 3899 | 0.443                   |
| HexaCB-130      | 7065 5603 5780 2080 25122 | 7238 5886 5578 1913 25258 | 0.568                   |
| HexaCB-132      | 399 326 252 5 1125 | 445 397 282 5 1134 | 0.143                   |
| HexaCB-134      | 25 5 50 5 183 | 35 5 47 5 168 | 0.203                   |
| HexaCB-135      | 419 342 318 5 1577 | 485 330 403 5 1587 | 0.382                   |
| HexaCB-137      | 10565 7132 9066 2996 41244 | 10646 7786 8734 2336 39991 | 0.889                   |
| HexaCB-138      | 96984 89163 52967 25546 240863 | 97685 84306 53897 23381 244647 | 0.990                   |
| HexaCB-139/149  | 635 452 619 15 2404 | 615 292 696 5 2303 | 0.568                   |
| HexaCB-141      | 328 255 246 5 1044 | 340 282 287 5 1169 | 0.716                   |
| HexaCB-146      | 32968 34220 16346 11603 83149 | 35211 31688 16262 9839 68936 | 0.086                   |
| HexaCB-147      | 724 567 463 5 1678 | 768 622 519 5 1806 | 0.527                   |
| HexaCB-151      | 1329 981 880 428 3402 | 1349 1008 1098 5 4265 | 0.258                   |
| HexaCB-153      | 200929 184176 106109 73832 516088 | 206380 180663 109234 59314 458743 | 0.501                   |
| HexaCB-163/164  | 48797 47157 25168 17426 113577 | 49567 47872 22738 15767 88552 | 0.694                   |
| HexaCB-165      | ND | ND | ND | ND |
Data analysis

To estimate the TEQ concentrations, we introduced ND (less than the detection limit) values to half values of the detection limit and calculated the TEQ concentrations based on the TEF values proposed by the WHO [23]. The statistical analysis was conducted using Wilcoxon signed-rank test in the software programs from Statistics Package for Social Sciences (version 22; IBM Armonk, NY, USA). Significant probabilities (p values) were calculated for the respective number of samples analyzed.

Results

The objective of the present study was to evaluate the effectiveness of colestamide on the individual congener concentrations of PCDDs, PCDFs, and PCBs in the blood of Yusho patients. Of the 36 Yusho patients who began the trial, 9 patients stopped administrating colestamide due to serious adverse effects, constipation or abdominal distension. Of the 27 remaining patients, we failed to collect a posttreatment blood sample from one patient due to cancellation of hospital visit. The individual congener concentrations of PCDDs, PCDFs and PCBs in the blood of 26 Yusho patients before the trial were compared with those after the trial (Tables 1 and 2).

The arithmetic mean TEQ concentrations of PCDDs, PCDFs, non-ortho PCBs, and mono-ortho PCBs in the blood of the 26 Yusho patients were 24, 82, 21, and 3.2 pg TEQ/g lipid, respectively, before the trial, and 24, 82, 22, and 3.1 pg TEQ/g lipid, respectively, after the trial. Total TEQ concentration of these dioxin-like compounds equaled 42–303 (mean: 130, median: 120) pg TEQ/g lipid before the trial, and 43–283 (mean: 132, median: 118) pg TEQ/g lipid after the trial, indicating that the concentrations before the trial were almost the same as those after the trial. Regarding the non-dioxin-like PCB concentrations, the sums of the concentrations of 58 PCB congeners in the blood before and after the trial were 321–2643 (mean: 957, median: 872) and 286–2007 (mean: 975, median: 806) ng/g lipid, respectively. The arithmetic mean concentrations of triCBs, tetraCBs, heptaCBs, octaCBs, nonaCBs, decaCBs, total TrCBs, total TeCBs, total PeCBs, total HxCB, total HpCBs, total OcCBs, total NoCBs, total DeCBs, total PCBs are shown in Table 2.

Table 2: Effect of colestamide on the individual congener concentrations of non-dioxin-like PCBs in the blood of Yusho patients (Continued)

| Congener | Before Trial | After Trial | % Change | SD | p-value |
|----------|-------------|-------------|----------|----|---------|
| HeptaCB-180 | 205779 | 201272 | 2.2 | 6087 | 0.67 |
| HeptaCB-181 | 53 | 292 | 433.9 | 71 | 0.03 |
| HeptaCB-182/187 | 76063 | 60684 | 20.3 | 14834 | 0.03 |
| HeptaCB-183 | 16843 | 14980 | 11.0 | 4733 | 0.01 |
| HeptaCB-191 | 3078 | 2922 | 4.8 | 2008 | 0.04 |
| OctaCB-194 | 31774 | 32293 | 1.7 | 22776 | 0.01 |
| OctaCB-195 | 7832 | 6835 | 12.5 | 5994 | 0.04 |
| OctaCB-196/203 | 17107 | 15138 | 12.6 | 11346 | 0.04 |
| OctaCB-198/201 | 14771 | 12536 | 16.9 | 11520 | 0.03 |
| OctaCB-200 | 659 | 485 | 28.0 | 607 | 0.01 |
| OctaCB-202 | 5432 | 3893 | 29.3 | 4532 | 0.01 |
| OctaCB-205 | 977 | 898 | 8.1 | 633 | 0.01 |
| NonaCB-206 | 5049 | 4561 | 9.6 | 2829 | 0.01 |
| NonaCB-207 | 922 | 755 | 17.2 | 572 | 0.01 |
| NonaCB-208 | 1877 | 1731 | 7.3 | 1209 | 0.01 |
| DecaCB-209 | 1857 | 1598 | 14.8 | 890 | 0.01 |
| Total TrCBs | 1792 | 1471 | 18.8 | 999 | 0.01 |
| Total TeCBs | 20023 | 17013 | 15.1 | 11246 | 0.01 |
| Total PeCBs | 31271 | 26027 | 16.9 | 19945 | 0.01 |
| Total HxCB | 402098 | 373141 | 7.6 | 196792 | 0.01 |
| Total HpCBs | 413979 | 401285 | 3.4 | 265364 | 0.01 |
| Total OcCBs | 78553 | 77549 | 1.3 | 55605 | 0.01 |
| Total NoCBs | 8749 | 6439 | 29.9 | 4416 | 0.01 |
| Total DeCBs | 1857 | 1598 | 14.8 | 890 | 0.01 |
| Total PCBs | 957422 | 871523 | 9.7 | 520304 | 0.01 |

ND (less than the detection limit) values introduced to half values of the detection limit and calculated the TEQ concentrations
SD standard deviation, CB chlorinated biphenyl
pentaCBs, hexaCBs, heptaCBs, octaCBs, and nonaCBs in the blood of Yusho patients were 1.8, 20, 31, 402, 414, 79, and 7.8 ng/g lipid, respectively, before the trial, and 1.9, 20, 33, 412, 420, 79, and 7.6 ng/g lipid, respectively, after the trial, indicating that concentrations of these PCBs compounds were also almost the same before and after the trial. These results indicated that the concentrations of PCDDs, PCDFs, dioxin-like PCBs and non-dioxin-like PCBs in the blood of Yusho patients were not significantly altered by the intervention with oral colestimide.

We previously reported that the concentrations of 1,2,3,6,7,8-hexaCDD, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, hexaCB-169, hexaCB-156, hexaCB-157, and heptaCB-189 in the blood of Yusho patients were higher than those of the normal controls [8, 9]. These can be considered the characteristic congeners in the blood of Yusho patients. 2,3,4,7,8-PentaCDF is recognized as the most important causative agent for subjective symptoms of Yusho. Blood levels before and after the trial were 48–636 (mean: 241, median: 191) and 49–613 (mean: 242, median: 205) pg TEQ/g lipid, respectively, indicating that the concentration did not significantly decrease with administration of colestimide. This was also the case for the concentrations of other characteristic congeners before and after the trial. Among congeners of PCDDs, PCDFs, dioxin-like PCBs, and non-dioxin-like PCBs, most congeners did not show statistically significant differences. According to these results, the therapeutic usefulness of colestimide in reducing the concentrations of PCDDs, PCDFs, and PCBs in blood of Yusho patients could not be confirmed.

Discussion

Over 48 years have passed since the outbreak of Yusho disease. However, some patients are still afflicted with intractable symptoms such as chloracne, general fatigue and neuropathy [12]. There are patients who continue to have much higher concentrations of dioxin-like compounds in their blood than unaffected persons. Moreover, the half-lives of blood concentrations of 2,3,4,7,8-pentaCDF have become long to near infinity in the majority of Yusho patients [24]. To reduce the concentrations of PCDDs, PCDFs, and PCBs in the blood of Yusho patients, our study group previously conducted a clinical trial using cholestyramine and rice bran fiber [19, 20]. Results of that study showed that the amounts of 2,3,4,7,8-pentaCDF in patients’ feces actually increased, although beneficial clinical effects were not apparent, possibly due to a short trial period. A recent study reported that colestimide can decrease the concentrations of PCDDs, PCDFs, and PCBs in blood [21, 22]. Eight male and two female healthy subjects were treated with colestimide (3 g/day) for 6 months. In this report, colestimide was effective for promoting excretion of dioxin-like compounds from the human body. Colestimide is a non-absorbable anion exchange resin and enhances excretion of cholesterol in feces by inhibiting absorption of food-derived cholesterol in the intestinal tract [25]. Based on this result, we designed a clinical trial with colestimide for Yusho patients. However, in the present study, we were unable to confirm a significant decrease in most congeners of PCDDs, PCDFs, and PCBs in the blood of Yusho patients. It is suggested that the PCDDs, PCDFs, and PCBs that have remained in the whole body of patients over the 45 years since the outbreak of Yusho are very difficult to excrete from the body. In the present trial, there may be many limitations such as a small number of participants, duration of administration period and dose of colestimide. Out of the 36 patients who participated in the trial, 9 patients experienced serious adverse effects (constipation or abdominal distension) by the repeated administration of colestimide. Therefore, we cannot recommend that elderly patients participate in clinical trial studies for such long periods as in the present study.

Conclusion

Although over 48 years have passed since the outbreak of Yusho, many patients still suffer various symptoms such as chloracne, general fatigue and neuropathy. The concentrations of causative dioxin-like compounds in their blood remain at high levels. We examined whether oral administration of colestimide could reduce the concentrations of PCDDs, PCDFs, and PCBs in the blood of Yusho patients. However, the effectiveness of colestimide on the concentrations of these dioxin-like compounds in the blood of Yusho patients could not be confirmed.

Abbreviations

PCDDs, polychlorinated dibenzo-p-dioxins; PCDFs, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls; WHO, World Health Organization; TEF, toxic equivalent factor.

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Availability of data and materials

We do not wish to share the data included in this manuscript. Patients who fulfilled the diagnostic criteria for Yusho established by the National Study Group for the Therapy of Yusho were eligible for this study. Therefore, we want to protect the patients’ identities and personal information.

Authors’ contributions

TT developed the analytical method, and drafted the initial manuscript. AK, MI and YT examined the data quality for analyses. CM and MF interpreted the results. MF coordinated the project. All authors approved the final manuscript.
Competition of interests
The authors declare that they have no competing interests.

Consent for publication
Patients were recruited at explanatory meetings conducted in Fukuoka and Nagasaki Prefectures. 50 Yusho patients were enrolled in this clinical trial, and 36 patients participated in the trial. Informed consent was obtained for study participation. We also confirmed their consent for publication of this manuscript.

Ethics approval and consent to participate
The study project was approved by the institutional ethics committee of Kyushu University Hospital (reference 18034).

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