

The Pharmacokinetics of Cromolyn and Ibuprofen in Healthy Elderly Volunteers

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Supplemental Table 1. Pharmacokinetic Analytical Methods

Assay	Sample Preparation	Methods	Linearity	Precision (% CV)	Accuracy (% Bias)	Stability
Cromolyn CSF	Cromolyn and the internal standard, cromolyn-d ₅ , were released from the human CSF by dilution.	LC-MS/MS Reversed phase HPLC C8 analytical column Applied Biosystems API5000 or API5500	Bias at LLOQ: 0.7% Bias above LLOQ: -1.2 to 1.1% Bioanalytical range: 0.100 to 10.0 ng/mL	Intra-assay: 6.8 to 7.3% (LLOQ) 1.0 to 7.4% (above LLOQ) Inter-assay: 6.7% (LLOQ) 2.9 to 6.3% (above LLOQ)	Intra-assay: -4.0 to -2.2% (LLOQ) 0.1 to 7.8% (above LLOQ) Inter-assay: -2.8% (LLOQ) 2.7 to 5.0% (above LLOQ)	Stable for 4 freeze/thaw cycles Stable at RT for 7.75 hours Stable for 141 days at -70°C
Cromolyn Plasma	Cromolyn and the internal standard, cromolyn-d ₅ , were released from the human plasma containing K2-EDTA by protein precipitation.	LC-MS/MS Reversed phase HPLC Diphenyl analytical column Applied Biosystems API5000 or API5500	Bias at LLOQ: 2.2% Bias above LLOQ: -4.2 to 4.0% Bioanalytical range: 10.0 to 2,000.0 ng/mL	Intra-assay: 3.5 to 6.8% (LLOQ) 2.5 to 5.7% (above LLOQ) Inter-assay: 5.2% (LLOQ) 3.3 to 4.1% (above LLOQ)	Intra-assay: -1.4 to 0.2% (LLOQ) -2.3 to 3.6% (above LLOQ) Inter-assay: -0.7% (LLOQ) -1.5 to 1.4% (above LLOQ)	Stable for 4 freeze/thaw cycles Stable at RT for 7.5 hours Stable for 187 days at -70°C
Ibuprofen CSF	Ibuprofen and the internal standard, ibuprofen-d ₃ , were extracted from human CSF using derivatization followed by liquid-liquid extraction.	LC-MS/MS Reversed phase HPLC C8 analytical column Applied Biosystems API4000	Bias at LLOQ: -0.5% Bias above LLOQ: -2.0 to 1.6% Bioanalytical range: 0.300 to 75.0 ng/mL	Intra-assay: 2.3 to 5.9% (LLOQ) 1.0 to 4.9% (above LLOQ) Inter-assay: 6.8% (LLOQ); 2.8 to 3.8% (above LLOQ)	Intra-assay: -12.4 to -0.4% (LLOQ) -7.4 to 3.3% (above LLOQ) Inter-assay: -5.4% (LLOQ) -5.8 to -0.6% (above LLOQ)	Stable for 4 freeze/thaw cycles Stable at RT for 7.25 hours Stable for 120 days at -70°C
Ibuprofen Plasma	Ibuprofen and the internal standard, ibuprofen-d ₃ , were released from the human plasma containing K2-EDTA by protein precipitation.	LC-MS/MS Reversed phase HPLC C18 analytical column Applied Biosystems API3000 or API4000	Bias at LLOQ: 0.2% Bias above LLOQ: -5.3 to 4.2% Bioanalytical range: 25.0 to 12,500 ng/mL	Intra-assay: 9.7 to 12.4% (LLOQ) 2.7 to 6.5% (above LLOQ) Inter-assay: 17.6% (LLOQ) 3.6 to 6.3% (above LLOQ)	Intra-assay: -17.6 to 16.2% (LLOQ) -2.8 to 9.5% (above LLOQ) Inter-assay: -0.2% (LLOQ) -1.4 to 5.4% (above LLOQ)	Stable for at least 4 freeze/thaw cycles Stable at RT for 8.0 hours Stable for 196 days at -70°C

CSF cerebral spinal fluid; CV coefficient of variation; HPLC high performance liquid chromatography; EDTA ethylenediaminetetraacetic acid; LC-MS/MS liquid chromatography-tandem mass spectroscopy; LLOQ lower limit of quantification; RT room temperature

Supplemental Table 2. Cromolyn Plasma Concentrations

Condition / Parameter	0 Minutes	5 Minutes	10 Minutes	15 Minutes	30 Minutes	1 Hour	2 Hours	4 Hours	6 Hours
Single Dose (17.1 mg), n	25	25	25	25	25	25	23	9	0
Mean (SD)	0.00 (0.000)	35.92 (32.492)	40.53 (32.420)	38.66 (27.396)	40.29 (28.928)	30.29 (15.962)	20.36 (10.558)	14.14 (4.384)	
%CV		90.45	79.99	70.86	71.80	52.70	51.86	31.00	
Median	0.00	26.90	32.70	35.00	29.50	25.30	17.20	12.10	
Range	0 - 0	0 - 130	0 - 133	0 - 108	14 - 117	13 - 81	10 - 54	10 - 22	
Double Dose (34.2 mg), n	24	24	24	24	24	24	24	19	10
Mean (SD)	0.00 (0.000)	73.57 (44.629)	87.32 (46.475)	88.18 (44.424)	77.75 (37.071)	67.07 (27.571)	40.53 (17.949)	21.88 (6.996)	14.93 (3.328)
%CV		60.66	53.22	50.38	47.68	41.11	44.28	31.97	22.29
Median	0.00	66.15	73.80	74.60	64.50	58.35	36.40	19.10	14.30
Range	0 - 0	15 - 213	30 - 236	34 - 223	35 - 172	33 - 122	18 - 88	13 - 36	10 - 19

BLLOQ below lower limit of quantification, *max* maximum, *min* minimum, *SD* standard deviation, *%CV* coefficient of variation ($100 \times SD / \text{Mean}$). Values reported in ng/mL. For concentrations, all BLLOQ values occurring prior to C_{\max} were replaced by '0', except for embedded BLLOQ values (between two measurable data points) which are treated as missing. Post- C_{\max} BLLOQ values were treated as missing.

Supplemental Table 3. Ibuprofen Plasma Concentrations

Condition / Parameter	0 Minutes	5 Minutes	10 Minutes	15 Minutes	30 Minutes	1 Hour	2 Hours	4 Hours	6 Hours
Single Dose (10 mg), n	24	24	24	23	23	23	23	23	23
Mean (SD)	3.14 (10.656)	7.06 (14.425)	44.09 (73.112)	189.61 (354.397)	389.52 (596.162)	655.22 (502.392)	670.83 (431.803)	368.57 (311.202)	202.17 (107.142)
%CV	339.17	204.37	165.82	186.91	153.05	76.68	64.37	84.44	53.00
Median	0.00	0.00	0.00	0.00	79.10	542.00	693.00	313.00	187.00
Range	0 - 39	0 - 43	0 - 234	0 - 1340	0 - 1780	0 - 1270	0 - 1970	0 - 1610	0 - 460
Double Dose (20 mg), n	24	23	24	24	24	24	24	24	24
Mean (SD)	5.70 (21.423)	9.19 (30.977)	19.41 (37.469)	182.49 (449.690)	716.72 (836.638)	1362.71 (952.757)	1442.50 (667.287)	774.21 (470.139)	486.17 (333.593)
%CV	375.56	337.02	193.01	246.42	116.73	69.92	46.26	60.73	68.62
Median	0.00	0.00	0.00	53.70	346.50	1355.00	1385.00	655.00	412.50
Range	0 - 100	0 - 144	0 - 154	0 - 2220	0 - 3220	0 - 3400	0 - 2870	386 - 2740	181 - 1800

BLLOQ below lower limit of quantification, *max* maximum, *min* minimum, *SD* standard deviation, *%CV* coefficient of variation ($100 \times SD / \text{Mean}$). Values reported in ng/mL. For concentrations, all *BLLOQ* values occurring prior to C_{max} are replaced by '0', except for embedded *BLLOQ* values (between two measurable data points) which are treated as missing. Post- C_{max} *BLLOQ* values are treated as missing.

Supplemental Table 4. Cromolyn CSF Concentrations

Condition / Parameter	0 Minutes	5 Minutes	30 Minutes	2 Hours	4 Hours
Single Dose (17.1 mg), n	6	6	6	6	6
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)	0.16 (0.069)	0.23 (0.077)
%CV				43.47	33.25
Median	0.00	0.00	0.00	0.13	0.22
Range	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.1 - 0.3	0.1 - 0.4
Double Dose (34.2 mg), n	7	7	6	7	7
Mean (SD)	0.00 (0.000)	0.13 (0.218)	0.05 (0.111)	0.28 (0.189)	0.31 (0.137)
%CV		171.77	244.95	67.48	44.24
Median	0.00	0.00	0.00	0.19	0.33
Range	0.0 - 0.0	0.0 - 0.5	0.0 - 0.3	0.1 - 0.6	0.2 - 0.5

BLLOQ below lower limit of quantification, *max* maximum, *min* minimum, *SD* standard deviation, *%CV* coefficient of variation ($100 \times SD / \text{Mean}$). Values reported in ng/mL. For concentrations, all BLLOQ values occurring prior to C_{max} are replaced by '0', except for embedded BLLOQ values (between two measurable data points) which are treated as missing. Post- C_{max} BLLOQ values are treated as missing

Supplemental Table 5. Ibuprofen CSF Concentrations

Condition / Parameter	0 Minutes	5 Minutes	30 Minutes	2 Hours	4 Hours
Single Dose (10 mg), n	6	6	6	6	6
Mean (SD)	0.00 (0.000)	0.10 (0.247)	0.18 (0.308)	2.61 (2.272)	2.15 (1.762)
%CV		244.95	166.78	87.15	81.84
Median	0.00	0.00	0.00	2.91	2.70
Range	0.0 - 0.0	0.0 - 0.6	0.0 - 0.7	0.0 - 5.2	0.0 - 4.0
Double Dose (20 mg), n	7	7	6	7	7
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.27 (0.356)	6.70 (4.676)	8.22 (3.064)
%CV			129.68	69.74	37.25
Median	0.00	0.00	0.17	5.48	8.05
Range	0.0 - 0.0	0.0 - 0.0	0.0 - 0.9	0.0 - 15.0	4.7 - 13.5

BLLOQ below lower limit of quantification, *max* maximum, *min* minimum, *SD* standard deviation, *%CV* coefficient of variation ($100 \times SD / \text{Mean}$). Values reported in ng/mL. For concentrations, all BLLOQ values occurring prior to C_{max} are replaced by '0', except for embedded BLLOQ values (between two measurable data points) which are treated as missing. Post- C_{max} BLLOQ values are treated as missing.