Supporting Information for

Dosing time optimization of antihypertensive medications by including the circadian rhythm in pharmacokinetic-pharmacodynamic models

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Figure A. Simulations and data for enalapril model. Panels on the left correspond to 7 a.m. dosing time and panels on the right to 7 p.m. dosing time. Figures A-B, amount available to be absorbed (Xu); C-D, enalapril concentration (data in black dots); E-F, enalaprilat concentration (data in green dots); G-H, SBP (data before treatment in light red dots and after treatment in dark red dots); I-J, DBP (data before treatment in light blue dots and after treatment in dark blue dots), in all figures the solid line represents the prediction of the model after treatment and the dotted line the prediction of the model before treatment. Data from Witte et al. [1].
**Figure B. Simulations and data for nifedipine model.** Panels on the left correspond to 8 a.m. dosing time and panels on the right to 7 p.m. dosing time. Figures A-B, amount available to be absorbed (Xu); C-D, nifedipine concentration (data in green dots); E-F, SBP (data before treatment in light red dots and after treatment in dark red dots); G-H, DBP (data before treatment in light blue dots and after treatment in dark blue dots), in all figures the solid line represents the prediction of the model after treatment and the dotted line the prediction of the model before treatment. Data from Lemmer et al. [2].
Figure C. Simulations and data for lisinopril model. Panels on the left correspond to 8 a.m. dosing time, panels in the middle to 4 p.m. dosing time and panels on the right to 10 p.m. dosing time. Figures A-B, amount available to be absorbed (Xu); C-D, lisinopril concentration (data in black dots); E-F, SBP; G-H, DBP (data before treatment in gray dots and after treatment in blue dots), in all figures the solid gray line represents the prediction of the model after treatment and the gray dotted line the prediction of the model before treatment. Data from Macchiarulo et al. [3].
Figure D. Parameter correlation matrices of all models. Figure A, amlodipine; B, nifedipine; C, telmisartan; D, olmesartan; E, valsartan; F, lisinopril; G, enalapril; H, ramipril; I, spirapril; J, perindopril.
Figure E. Model simulation and BP data of dipper and non-dipper subjects. Figure A, dipper subjects; Figure B, non-dipper subjects. SBP and DBP is showed in red and blue dots, respectively. In both figures the dotted line represents the prediction of the model before treatment. Data from Hermida et al. [4].
Figure F. Relationship between dosing time and DBP dipper percentage, average DBP reduction (DBP\textsubscript{reduced}), and average DBP peaks reduction (DBP\textsubscript{peaks}) for amlodipine, nifedipine, telmisartan, olmesartan, and valsartan. Panels on the left show the results for dipper subjects and those on the right for non-dipper subjects. Figure A-B, amlodipine; C-D, nifedipine; E-F, olmesartan; G-H, telmisartan; I-J, valsartan. Dosing time is represented in colors from 0 to 24 hours after awakening (colorbar).
Figure G. Relationship between dosing time and DBP dipper percentage, average DBP reduction (DBP_{reduced}), and average DBP peaks reduction (DBP_{peaks}) for lisinopril, enalapril, ramipril, spirapril and perindopril. Panels on the left show the results for dipper subjects and those on the right for non-dipper subjects. Figure A-B, lisinopril; C-D, enalapril; E-F, ramipril; G-H, spirapril; I-J, perindopril. Dosing time is represented in colors from 0 to 24 hours after awakening (colorbar).
Table A. Estimated parameters for systolic and diastolic blood pressure before treatment for amlodipine, nifedipine, valsartan, olmesartan, and telmisartan (AM/PM experimental groups).

|       | Amlodipine | Nifedipine | Valsartan | Olmesartan | Telmisartan |
|-------|------------|------------|-----------|------------|-------------|
|       | AM/PM      | CI *       | AM/PM     | CI *       | AM          | CI *       | PM      | CI *       | AM          | CI *       | PM      | CI *       |
| $M$   | 153.012    | 440.7      | 133.737   | 309.46     | 141.387     | 133.02     | 134.212 | 142.37     | 121.029     | 89.957     | 125.628 | 110.22     |
| $A_{12}$ | 5.772   | 14.199     | 4.679     | 9.966      | 5.502       | 4.599      | 4.048    | 3.743      | 7.18        | 4.078      | 5.081   | 3.916      |
| $O_{12}$ | -54.058 | 1.097      | -42.555   | 0.661      | -29.848     | 0.326      | -23.486  | 0.396      | -36.377     | 0.252      | -36.161 | 0.312      |
| $A_{24}$ | 12.816  | 35.282     | 10.794    | 24.925     | 5.416       | 5.277      | 3.245    | 3.509      | 11.542      | 7.488      | 8.992   | 7.754      |
| $O_{24}$ | -53.854 | 0.611      | -53.95    | 0.413      | -98.113     | 0.22       | -98.199  | 0.3        | -123.3      | 0.148      | -110.77 | 0.19       |
| $k_{out_1}$ | 1.095   | 3.154      | 1.112     | 2.58       | 1.024       | 0.965      | 0.979    | 1.039      | 0.942       | 0.631      | 0.968   | 0.85       |
| $k_{out_2}$ | 1.689   | 4.864      | 2.002     | 4.632      | 1.664       | 1.568      | 1.58     | 1.678      | 1.48        | 0.99       | 1.531   | 1.345      |

* Confidence Interval (CI) for each parameter, the CI units are the same as the corresponding parameter value.
Table B. Estimated parameters for systolic and diastolic blood pressure before treatment for lisinopril, ramipril, enalapril, spirapril and perindopril (AM/PM experimental groups).

| Parameter | Lisinopril | Ramipril | Enalapril | Spirapril | Perindopril |
|-----------|------------|----------|-----------|-----------|-------------|
|           | AM/PM  | CI *     | AM  | CI *     | PM  | CI *     | AM  | CI *     | PM  | CI *     | AM/PM | CI *     |
| $M$       | 144.576 | 156.09   | 141.014 | 114.08   | 142.991 | 134.02   | 146.369 | 241.76   | 142.636 | 68.34   | 135.04 | 123.62   | 144.727 | 221.51   |
| $A_{12}$  | 9.413   | 9.02     | 6.929   | 5.126    | 5.774   | 4.654    | 7.758    | 11.155   | 7.36     | 3.149    | 5.611   | 4.464    | 4.724    | 6.623    |
| $O_{12}$  | -98.079 | 0.391    | -48.718 | 0.266    | -48.901 | 0.347    | -54.53   | 0.619    | -61.296  | 0.143    | -55.1   | 0.325    | -35.449  | 0.567    |
| $A_{24}$  | 12.222  | 12.928   | 14.432  | 11.585   | 12.636  | 11.358   | 17.037   | 26.594   | 11.297   | 5.5      | 9.741   | 8.693    | 8.923    | 13.571   |
| $O_{24}$  | -28.338 | 0.237    | -54.184 | 0.148    | -54.204 | 0.192    | -53.894  | 0.322    | -10.205  | 0.091    | -16.579 | 0.188    | -53.485  | 0.345    |
| $k_{out1}$| 1.055   | 1.139    | 1.106   | 0.897    | 1.106   | 1.037    | 1.001    | 1.653    | 1.12     | 0.538    | 1.046   | 0.958    | 0.973    | 1.491    |
| $k_{out2}$| 1.587   | 1.716    | 1.685   | 1.364    | 1.687   | 1.58     | 1.716    | 2.828    | 1.735    | 0.834    | 1.654   | 1.515    | 1.592    | 2.439    |

* Confidence Interval (CI) for each parameter, the CI units are the same as the corresponding parameter value.
Table C. Fixed parameters for PK-PD models.

|                | Amlodipine | Nifedipine | Valsartan | Olmesartan | Telmisartan | Lisinopril | Ramipril | Enalapril | Spirapril | Perindopril |
|----------------|------------|------------|-----------|------------|-------------|------------|----------|-----------|-----------|-------------|
| **IC$_{50}$ (nM)** | 0.777 [5]  | 1.42 [5]   | 0.24 [6]  | 0.058 [6]  | 0.17 [6]    | 7.46 [7]   | 0.295*[8]| 0.676*[9]| 0.373*[10]| 0.866*[11] |
| **F (%)**      | 64 [12]    | 89 [13]    | 23 [14]   | 28.6 [15]  | 43 [14]     | 25 [16]    | 50-60**[17]| 60 [17]  | 50 [16]   | 95 [18]     |
| **Vd (L)**     | 1425.2 [12]| 139.43 [19]| 17 [20]   | 34.9 [21]  | 500 [14]    | 124 [22]   | -        | -         | 28 [16]   | 6.4 [23]    |
| **F/Vd**       | 0.000449   | 0.00638    | 0.0132    | 0.00819    | 0.00086     | 0.00202    | -        | -         | 0.0179    | 0.1484      |

* IC$_{50}$ value of active metabolites (ramiprilat, enalaprilat, spiraprilat, perindoprilat).
** The average value (55%) was used.
Table D. Estimated parameters for non-prodrug selected models.

|          | Amlodipino | Nifedipino | Valsartan | Olmesartan | Telmisartan | Lisinopril |
|----------|------------|------------|-----------|------------|-------------|------------|
|          | value      | CI *       | value     | CI *       | value       | CI *       | value     | CI *       | value     | CI *       |
| $K_a$    | 0.01       | 0.003      | 8.667     | 0.969      | 0.048       | 0.004      | 0.084     | 0.003      | 0.086     | 0.004      | 0.039      | 0.002      |
| $K_e$    | 0.415      | 0.098      | 0.498     | 0.7        | 408.161     | 25.745     | 24.088    | 1.455      | 6.729     | 0.359      | 0.637      | 0.041      |
| $A_a$    | 0.01       | 0.003      | 6.399     | 1.018      | 0.04        | 0.004      | 0.073     | 0.004      | 0.078     | 0.006      | -48.919    | 0.238      |
| $O_a$    | -45.571    | 0.399      | -40.051   | 0.052      | -87.101     | 0.085      | -100.104  | 0.057      | -105.507  | 0.068      | 0.986      | 0.263      |
| $A_e$    | 0.39       | 0.113      | 0.254     | 0.129      | 358.152     | 30.059     | 19.421    | 1.737      | 6.399     | 0.434      | 0.475      | 0.09       |
| $O_e$    | -6.914     | 0.254      | -10.582   | 3.072      | -4.882      | 0.079      | -105.448  | 0.076      | -10.67    | 0.048      | -16.977    | 0.171      |
| $I_{max}$| 0.178      | 0.027      | 0.044     | 0.023      | 0.229       | 0.008      | 0.169     | 0.023      | 0.14      | 0.019      | 0.345      | 0.078      |
| $n$      | 0.683      | 0.248      | 3.314     | 29.826     | 1.222       | 0.154      | 0.617     | 0.386      | 0.709     | 0.46       | 0.026      | 0.005      |

* Confidence Interval (CI) for each parameter, the CI units are the same as the corresponding parameter value.
Table E. Estimated parameters for prodrug selected models.

|             | Ramipril |             | Enalapril |             | Spirapril |             | Perindopril |
|-------------|----------|-------------|-----------|-------------|-----------|-------------|-------------|
|             | value    | CI *        | value     | CI *        | value     | CI *        | value       | CI *        |
| $K_a$       | 0.079    | 0.004       | 0.77      | 0.001       | 0.046     | 0.003       | 0.1         | 0.003       |
| $K_{e_1}$   | 1.06     | 0.252       | 0.74      | 0.023       | 3         | 0.212       | 1.284       | 0.052       |
| $K_{e_2}$   | 3.364    | 2.626       | 0.127     | 0.002       | 1.96      | 1.498       | 0.372       | 0.103       |
| $K_m$       | 0.032    | 0.025       | 0.288     | 0.019       | 0.125     | 0.096       | 0.013       | 0.004       |
| $A_a$       | 0.079    | 0.008       | 0.595     | 0.008       | 0.024     | 0.003       | -           | -           |
| $O_a$       | -67.451  | 0.098       | -107.938  | 0.01        | -30.633   | 0.095       | -           | -           |
| $A_{e_1}$   | 0.984    | 0.199       | -         | -           | -         | -           | -           | -           |
| $O_{e_1}$   | -85.747  | 0.143       | -         | -           | -         | -           | -           | -           |
| $A_{e_2}$   | -        | -           | 0.013     | 0.009       | 0.946     | 0.812       | 0.356       | 0.031       |
| $O_{e_2}$   | -        | -           | -60.056   | 0.701       | -30.193   | 0.146       | -3.936      | 0.164       |
| $F/V_d$ **  | 0.171    | 0.041       | 0.018     | 0.001       | -         | -           | -           | -           |
| $I_{max}$   | 0.166    | 0.009       | 0.171     | 0.022       | 0.387     | 0.021       | 0.103       | 0.016       |
| $n$         | 1.505    | 0.338       | 0.293     | 0.148       | -         | -           | 2.699       | 1.751       |

* Confidence Interval (CI) for each parameter, the CI units are the same as the corresponding parameter value.

** Estimated parameter for enalapril neither ramipril since there are no reported values of volume of distribution (Vd).
Table F. Estimated parameters for systolic and diastolic blood pressure before treatment for dipper and non-dipper patterns†.

|        | Dipper  |   | Non-dipper |   |
|--------|---------|---|------------|---|
|        | value   | CI * | value      | CI * |
| $M$    | 129.55  | 82.221 | 144.92     | 262.563 |
| $A_{12}$ | 7.33    | 3.97  | 5.73       | 8.831  |
| $O_{12}$ | -35.73  | 0.246 | -35.67     | 0.619  |
| $A_{24}$ | 14.93   | 9.038 | 4.64       | 7.919  |
| $O_{24}$ | -53.96  | 0.14  | -53.61     | 0.401  |
| $k_{out_1}$ | 1.02   | 0.646 | 1.11       | 2.003  |
| $k_{out_2}$ | 1.61   | 1.02  | 1.79       | 3.246  |

† Parameters were adjusted to equations 1 and 2 using blood pressure data of dipper and non-dipper hypertensive subjects from the work of Hermida et al.[4].

* Confidence Interval (CI) for each parameter, the CI units are the same as the corresponding parameter value.
Table G. Dosing times after awakening for maximum ($T_{\text{max}}$) and minimum ($T_{\text{min}}$) values of dipper percentage (Dip), SBP average reduction ($\text{SBP}_{\text{reduced}}$), and SBP average peaks reduction ($\text{SBP}_{\text{peaks}}$) for dipper subjects.

| Drug/ prodrug | Dipper Percentage | Average Reduction | Average Peaks Reduction (mmHg) |
|---------------|-------------------|-------------------|--------------------------------|
|               | Dip min (%)       | $T_{\text{min}}$ (hh:mm) | Dip max (%)                   | $T_{\text{max}}$ (hh:mm) | $\Delta$Dip (%) | $\text{SBP}_{\text{reduced}}$ min (mmHg) | $T_{\text{min}}$ (hh:mm) | $\text{SBP}_{\text{reduced}}$ max (mmHg) | $\Delta$SBP reduced (mmHg) | $\text{SBP}_{\text{peaks}}$ min (mmHg) | $T_{\text{min}}$ (hh:mm) | $\text{SBP}_{\text{peaks}}$ max (mmHg) | $T_{\text{max}}$ (hh:mm) | $\Delta$SBP peaks (mmHg) |
| Amlodipino    | 12.63             | 00:01             | 13.22                          | 13:24                          | 0.59               | 7.71                          | 16:36                                      | 7.87                          | 01:21                          | 0.16                           | 9.15                          | 14:27                                      | 9.54                          | 00:47                          | 0.39                           |
| Nifedipino    | 14.2              | 23:55             | 18.92                          | 13:30                          | 4.72               | 1.34                          | 06:22                                      | 2.59                          | 15:31                          | 1.25                           | 0.92                          | 12:58                                      | 2.98                          | 23:59                          | 2.06                           |
| Lisinopril    | 15.27             | 21:49             | 19.44                          | 13:06                          | 4.17               | 11.54                         | 04:04                                      | 12.87                         | 15:29                          | 1.33                           | 11.13                         | 11:47                                      | 12.65                         | 19:29                          | 1.52                           |
| Enalapril     | 10.09             | 22:25             | 12.54                          | 09:24                          | 2.45               | 15.18                         | 16:45                                      | 15.45                         | 06:16                          | 0.27                           | 15.64                         | 13:27                                      | 16.85                         | 23:12                          | 1.21                           |
| Ramipril      | 13.75             | 23:06             | 21.32                          | 12:25                          | 7.57               | 9.16                          | 03:14                                      | 11.87                         | 14:21                          | 2.71                           | 8.72                          | 09:05                                      | 11.39                         | 16:59                          | 2.67                           |
| Perindopril   | 15.22             | 00:01             | 19.78                          | 11:54                          | 4.56               | 4.11                          | 19:11                                      | 6.53                          | 07:34                          | 2.42                           | 1.99                          | 14:47                                      | 4.4                           | 05:52                          | 2.41                           |
| Spirapril     | 13.98             | 22:48             | 19.38                          | 13:31                          | 5.4                | 8.94                          | 06:19                                      | 10.2                          | 18:42                          | 1.26                           | 8                             | 12:16                                      | 11.2                          | 21:41                          | 3.2                            |
| Telmisartan   | 15.06             | 23:36             | 18.51                          | 13:01                          | 3.45               | 10.69                         | 05:26                                      | 12.11                         | 17:38                          | 1.42                           | 10.36                         | 08:11                                      | 12.59                         | 20:29                          | 2.23                           |
| Olmesartan    | 15.37             | 23:42             | 19                             | 13:07                          | 3.63               | 13.81                         | 09:06                                      | 15.61                         | 21:45                          | 1.8                            | 13.06                         | 10:52                                      | 16.52                         | 22:47                          | 3.46                           |
| Valsartan     | 16.05             | 23:42             | 22.3                           | 13:49                          | 6.25               | 12.49                         | 07:03                                      | 14.59                         | 19:35                          | 2.1                            | 10.67                         | 11:47                                      | 14.86                         | 22:29                          | 4.19                           |
Table H. Dosing times after awakening for maximum (Ta\text{max}) and minimum (Ta\text{min}) values of dipper percentage (Dip), DBP average reduction (DBP\text{reduced}) and DBP average peaks reduction (DBP\text{peaks}) for dipper subjects.

| Drug/prodrug | Dip\text{min} (%) | Ta\text{min} (hh:mm) | Dip\text{max} (%) | Ta\text{max} (hh:mm) | Δ Dip (%) | DBP\text{reduced,min} (mmHg) | Ta\text{min} (hh:mm) | DBP\text{reduced,max} (mmHg) | Ta\text{max} (hh:mm) | Δ DBP\text{reduced} (mmHg) | DBP\text{peaks,min} (mmHg) | Ta\text{min} (hh:mm) | DBP\text{peaks,max} (mmHg) | Ta\text{max} (hh:mm) | Δ DBP\text{peaks} (mmHg) |
|--------------|-------------------|----------------------|-------------------|----------------------|-----------|-----------------------------|-------------------|-----------------------------|-------------------|---------------------------|-----------------------------|-------------------|-----------------------------|-------------------|-------------------------|
| Amlodipino   | 13.54             | 00:01                | 14.11             | 13:24                | 0.57      | 4.89                        | 16:32             | 4.99                        | 01:21             | 0.1                       | 5.81                        | 15:11             | 6.07                        | 00:47             | 0.26                    |
| Nifedipino   | 14.59             | 00:00                | 19.35             | 13:43                | 4.76      | 0.85                        | 06:22             | 1.64                        | 15:31             | 0.79                      | 0.57                        | 12:53             | 1.92                        | 23:59             | 1.35                    |
| Lisinopril   | 15.96             | 22:19                | 20.26             | 13:18                | 4.3       | 7.31                        | 04:04             | 8.16                        | 15:29             | 0.85                      | 7.06                        | 12:06             | 8.03                        | 19:31             | 0.97                    |
| Enalapril    | 10.8              | 22:43                | 13.34             | 09:54                | 2.54      | 9.63                        | 16:45             | 9.8                         | 06:15             | 0.17                      | 9.92                        | 13:27             | 10.72                       | 23:12             | 0.8                     |
| Ramipril     | 13.66             | 23:12                | 21.55             | 12:49                | 7.89      | 5.81                        | 03:04             | 7.53                        | 14:21             | 1.72                      | 5.54                        | 08:59             | 7.22                        | 16:54             | 1.68                    |
| Perindopril  | 15.48             | 00:36                | 20.17             | 12:13                | 4.69      | 2.61                        | 19:11             | 4.14                        | 07:34             | 1.53                      | 1.24                        | 14:36             | 2.78                        | 05:52             | 1.54                    |
| Spirapril    | 13.99             | 23:00                | 19.68             | 13:49                | 5.69      | 5.67                        | 06:19             | 6.47                        | 18:42             | 0.8                       | 5.06                        | 12:29             | 7.14                        | 21:30             | 2.08                    |
| Telmisartan  | 15.11             | 23:42                | 18.73             | 13:43                | 3.62      | 6.78                        | 05:26             | 7.68                        | 17:51             | 0.9                       | 6.58                        | 08:11             | 7.99                        | 20:54             | 1.41                    |
| Olmesartan   | 15.42             | 23:48                | 19.21             | 13:37                | 3.79      | 8.76                        | 09:06             | 9.9                         | 21:45             | 1.14                      | 8.31                        | 11:00             | 10.51                       | 22:43             | 2.2                     |
| Valsartan    | 16.2              | 23:48                | 22.79             | 14:13                | 6.59      | 7.92                        | 07:03             | 9.25                        | 19:35             | 1.33                      | 6.77                        | 11:54             | 9.47                        | 22:18             | 2.7                     |
Table I. Dosing times after awakening for maximum ($T_{a_{\text{max}}}$) and minimum ($T_{a_{\text{min}}}$) values of dipper percentage (Dip), SBP average reduction ($\Delta \text{SBP}_{\text{reduced}}$), and SBP average peaks reduction ($\Delta \text{SBP}_{\text{peaks}}$) for non-dipper subjects.

| Drug/prodrug | Dipper Percentage | Average Reduction (mmHg) | Average Peaks Reduction (mmHg) |
|--------------|-------------------|-------------------------|-------------------------------|
|              | $\text{Dip}_{\text{min}}$ | $T_{a_{\text{min}}}$ | $\Delta \text{Dip}$ | $\text{SBP}_{\text{reduced, min}}$ | $T_{a_{\text{min}}}$ | $\Delta \text{SBP}_{\text{reduced, max}}$ | $\text{SBP}_{\text{peaks, min}}$ | $T_{a_{\text{max}}}$ | $\Delta \text{SBP}_{\text{peaks, max}}$ |
| Amiodipino   | 3.08               | 23:07                   | 3.55 | 14:24 | 0.47 | 7.85 | 16:25 | 8 | 01:49 | 0.15 | 8.6 | 15:00 | 8.94 | 23:49 | 0.34 |
| Nifedipino   | 3.68               | 23:54                   | 8.93 | 13:31 | 5.25 | 1.29 | 06:31 | 2.8 | 15:17 | 1.51 | 1.17 | 05:11 | 3.24 | 21:56 | 2.07 |
| Lisinopril   | 5.46               | 21:37                   | 10.15 | 13:12 | 4.69 | 11.93 | 03:43 | 13.46 | 15:09 | 1.53 | 11.53 | 05:06 | 13.27 | 18:11 | 1.74 |
| Enalapril    | 2.37               | 22:19                   | 4.94 | 09:30 | 2.57 | 15.63 | 21:26 | 15.92 | 06:15 | 0.29 | 15.7 | 14:02 | 16.61 | 21:56 | 0.91 |
| Ramipril     | 3.25               | 22:54                   | 11.72 | 12:37 | 8.47 | 9.41 | 03:05 | 12.45 | 14:09 | 3.04 | 8.23 | 04:11 | 11.41 | 16:11 | 3.18 |
| Perindopril  | 5.87               | 00:00                   | 10.98 | 12:01 | 5.11 | 4.41 | 19:22 | 6.97 | 07:54 | 2.56 | 3.26 | 15:11 | 5.61 | 08:18 | 2.35 |
| Spirapril    | 3.46               | 22:42                   | 9.58 | 13:37 | 6.12 | 9.25 | 05:43 | 10.56 | 18:00 | 1.31 | 8.73 | 12:43 | 11.51 | 20:20 | 2.78 |
| Telmisartan  | 4.73               | 23:30                   | 8.58 | 13:25 | 3.85 | 11.06 | 05:18 | 12.54 | 17:17 | 1.48 | 10.28 | 05:11 | 12.68 | 19:35 | 2.4  |
| Olmesartan   | 5.05               | 23:36                   | 9.1  | 13:25 | 4.05 | 14.35 | 08:45 | 16.1 | 21:39 | 1.75 | 13.92 | 11:33 | 16.73 | 21:46 | 2.81 |
| Valsartan    | 5.84               | 23:42                   | 12.89 | 14:01 | 7.05 | 13.02 | 06:35 | 15.15 | 19:16 | 2.13 | 11.86 | 05:28 | 15.66 | 21:23 | 3.8  |
Table J. Dosing times after awakening for maximum (\(T_{a_{\text{max}}}\)) and minimum (\(T_{a_{\text{min}}}\)) values of dipper percentage (Dip), DBP average reduction (\(\Delta\text{DBP}_{\text{reduced}}\)), and DBP average peaks reduction (\(\Delta\text{DBP}_{\text{peaks}}\)) for non-dipper subjects.

| Drug/prodrug | Dip\(_{\text{min}}\) (%) | \(T_{a_{\text{min}}}\) (hh:mm) | Dip\(_{\text{max}}\) (%) | \(T_{a_{\text{max}}}\) (hh:mm) | \(\Delta\text{Dip}\) (%) | \(\Delta\text{DBP}_{\text{reduced}}\) (mmHg) | \(\Delta\text{DBP}_{\text{peaks}}\) (mmHg) |
|--------------|--------------------------|---------------------------------|--------------------------|-----------------------------|--------------------------|---------------------------|---------------------------|
| Amlodipino   | 3.34                     | 23:37                           | 3.84                     | 14:24                        | 0.5                      | 4.85                      | 16:25                     | 4.94                      | 01:49                     | 0.09                      | 5.31                      | 15:26                     | 5.52                      | 23:40                     | 0.21                      |
| Nifedipino   | 3.7                      | 23:54                           | 9                        | 13:49                        | 5.3                      | 0.8                       | 06:31                     | 1.73                      | 15:17                     | 0.93                      | 0.66                      | 05:12                     | 2.05                      | 21:52                     | 1.39                      |
| Lisinopril   | 5.69                     | 22:13                           | 10.55                    | 13:30                        | 4.86                     | 7.37                      | 03:43                     | 8.31                      | 15:09                     | 0.94                      | 7.11                      | 05:04                     | 8.24                      | 18:16                     | 1.13                      |
| Enalapril    | 2.43                     | 22:37                           | 5.11                     | 10:00                        | 2.68                     | 9.66                      | 21:15                     | 9.84                      | 06:15                     | 0.18                      | 9.7                       | 14:02                     | 10.29                     | 21:46                     | 0.59                      |
| Ramipril     | 2.94                     | 23:00                           | 11.73                    | 13:01                        | 8.79                     | 5.81                      | 03:05                     | 7.69                      | 14:09                     | 1.88                      | 4.99                      | 04:10                     | 7.04                      | 16:10                     | 2.05                      |
| Perindopril  | 5.84                     | 00:30                           | 11.11                    | 12:19                        | 5.27                     | 2.72                      | 19:22                     | 4.3                       | 07:54                     | 1.58                      | 2.01                      | 15:04                     | 3.53                      | 08:13                     | 1.52                      |
| Spirapril    | 3.27                     | 23:00                           | 9.67                     | 13:55                        | 6.4                      | 5.71                      | 05:31                     | 6.52                      | 18:00                     | 0.81                      | 5.39                      | 12:51                     | 7.18                      | 20:22                     | 1.79                      |
| Telmisartan  | 4.57                     | 23:36                           | 8.59                     | 13:55                        | 4.02                     | 6.83                      | 05:27                     | 7.75                      | 17:17                     | 0.92                      | 6.31                      | 05:04                     | 7.85                      | 19:34                     | 1.54                      |
| Olmesartan   | 4.9                      | 23:42                           | 9.11                     | 13:55                        | 4.21                     | 8.87                      | 08:45                     | 9.94                      | 21:39                     | 1.07                      | 8.64                      | 12:04                     | 10.38                     | 21:40                     | 1.74                      |
| Valsartan    | 5.8                      | 23:48                           | 13.2                     | 14:19                        | 7.4                      | 8.04                      | 06:34                     | 9.36                      | 19:16                     | 1.32                      | 7.3                       | 05:10                     | 9.76                      | 21:16                     | 2.46                      |
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