Application of a mechanism-based population pharmacodynamic model on the time-course of *ex-vivo* platelet aggregation when naproxen and aspirin are administered alone and in combination

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Abstract

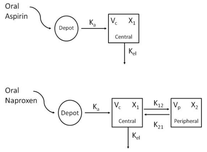
Purpose: To apply a mechanism-based, population pharmacodynamic model to the inhibitory effect of naproxen on the reversible inactivation of cyclooxygenase-1 (COX-1) by aspirin.

Methods: Two separate, complete three-way crossover studies were conducted. In both studies, eleven patients received 325 mg of aspirin, either 220 mg or 440mg of naproxen sodium and co-administration of both naproxen and aspirin. Whole blood platelet aggregometry was utilized to measure the aggregatory response of platelets in the presence of both collagen (1µg/ml) and arachidonic acid (0.5 mM) at 0, 2, 4, 8, 12, 24, 48 and 72 hours after drug administration. Pharmacokinetic parameters from the literature were utilized to simulate expected concentrations of drug within each subject. Pharmacodynamic modeling of the aggregatory response was analyzed using ADAPT V maximization likelihood expectation maximization (MLEM) algorithm using an additive error model.

Results: Inhibition of platelet aggregation after administration of aspirin occurred at 2 h and platelet function returned to baseline between 72-96 h. Following administration of naproxen alone, inhibition of platelet aggregation occurred at 2 h and platelet function returned to baseline between 8-24 h. Platelet aggregation after concomitant administration of aspirin and naproxen occurred in 2 h and returned to baseline function between 12-24 h. The final pharmacodynamic model was based the turnover of COX-1(k_{out}) and integrates the irreversible effect of aspirin (K) with the reversible effect of naproxen binding on COX-1 activity. Fitted parameter values for K (0.102 h^{-1}(10.8% RSE)) and k_{out} (0.022 (19.3%RSE)), with the standard deviation of inter-individual variability equal to 0.0093$(mg/L)^{-1}•h^{-1}$ and 0.006 h^{-1} and respectively, were found with the current pharmacodynamic model.

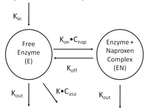
Conclusion: A mechanism based-pharmacodynamic model has been applied to a concomitant dose of naproxen and aspirin. This study suggests that naproxen has an inhibitory effect on the time-course of aspirin based anti-platelet effect.

Methods



Parameter	Population estimate
Aspirin model	
K_a (h^{-1})	1.1
k_{el}(h^{-1})	2.1
V_c (V/F) (L)	10
Naproxen model	
K_a (h^{-1})	1.98
k_{12} (h^{-1})	0.147
k_{21} (h^{-1})	0.198
k_{el}(h^{-1})	0.097
V_c (V/F) (L)	3.35

Pharmacokinetic parameters were fixed to literature values and served as the driving function for the pharmacodynamic analysis[1,2].



$$\frac{dE}{dt} = k_{in} - k_{out} \bullet E - K \bullet C_{asa} \bullet E - k_{on} \bullet C_{nap} + k_{off} \bullet EN \quad (1)$$

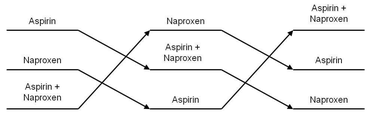
$$\frac{dEN}{dt} = k_{on} \bullet C_{nap} \bullet E - k_{off} \bullet EN - k_{out} \bullet EN \quad (2)$$

$$R = (E + EN) \bullet (1 - \beta \bullet C_{nap}) \quad (3)$$

$$k_{in} = R_0 \bullet k_{out} \quad (4)$$

Mechanism-based pharmacodynamic model[3] of COX-1 (enzyme) inhibition by aspirin and naproxen. C_{asa} = aspirin plasma concentration; C_{nap} = naproxen plasma concentrations; E= free enzyme; EN = enzyme-naproxen complex; K = second-order rate constant of irreversible enzyme inactivation by aspirin; k_{in} = zero-order production rate constant; k_{out} = first-order elimination rate constant; k_{on} = enzyme and naproxen association rate constant; k_{off} = enzyme and naproxen dissociation rate constant. The above model was fit to *ex vivo* platelet aggregometry data using ADAPT5 Maximum Likelihood Expectation Maximization (MLEM) algorithm. The rate of change of free enzyme (E) and naproxen-bound enzyme (EN) are described by the following differential equations (1) and (2). A linear transduction function was used to characterize the relationship between reversible enzyme binding kinetics and the anti-platelet effect of naproxen (3). The production rate constant (k_{in}) was fixed to a product of the turnover rate constant (k_{out}) and baseline aggregometry values (R_0)(4). Each patient baseline aggregometry (R_0) was fixed to a patient specific value in each study arm.

Clinical Study



Sampling Strategy
0, 2, 4, 6, 8, 12, 24, 48, 72,96 h post treatment. Sampling complete when return to baseline resistance (0 h) is achieved.

Figure 1: Randomized three way-cross over scheme. Platelet aggregation in whole blood samples was measured using an impedance aggregometer. Platelet aggregation was stimulated by collagen (1 µg/mL). Sampling for each study period is listed above, and each study period was separated by a washout period (arrows).

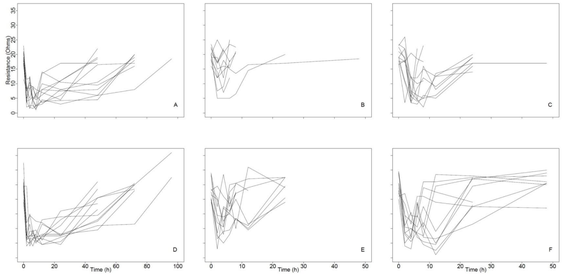


Figure 2: Time course of *ex vivo* whole blood aggregometry induced by collagen (1 µg/mL) following oral administration of aspirin (325 mg) (A & D), naproxen (220 mg) alone (B), naproxen (440 mg) alone (E), concomitant administration of aspirin (325 mg) and naproxen (220 mg) (D) and aspirin (325 mg) and naproxen (440 mg) (F).

Table I. Area under the effect curve for aspirin, naproxen and combination therapy

Therapy	Median (Ohms•h)	Interquartile Range (Ohms•h)
Aspirin	587	506 - 848
Naproxen	41.5	19.3 - 131
Aspirin & Naproxen	162	80.4 – 248

$$AUEC = \sum \frac{\Delta E_1 + \Delta E_2}{2} \bullet (t2 - t1) \quad (5)$$

The magnitude of effect was measured by subtracting the baseline platelet aggregometry value for a given individual from values observed during pharmacological treatment: $\Delta E_t = (R_0 - R_t)$. Kruskal-Wallis ANOVA using Bonferroni correction indicates all study periods statistically differ from one another ($p<0.015$).

Final Model Parameters

Table II. Final estimated pharmacodynamic model parameters

Parameter	Population estimate	(%RSE)	Inter-individual variability, %CV	(%RSE)
Structural model				
k_{out} (h^{-1})	0.022	19.3	25.4	125
K $(mg/L)^{-1}•h^{-1}$	0.102	10.8	11.0	16.8
β $(mg/L)^{-1}$	0.005	27.8	49.1	23.7
k_{off} (h^{-1})	42.0	46.0	130	60.8
k_{on} $(µmol/L)^{-1}•h^{-1}$	2.22	-	-	-
Residual Error				
σ_{add} (ohms)	4.35	4.61		

(-) not estimated; (K) second-order rate constant of irreversible enzyme inactivation by aspirin; (k_{in}) zero-order production rate constant; (k_{out}) first-order elimination rate constant; (k_{on}) enzyme and naproxen association rate constant; (k_{off}) enzyme and naproxen dissociation rate constant; (σ_{add}) additive error term (expressed as a standard deviation).

Visual Predictive Check

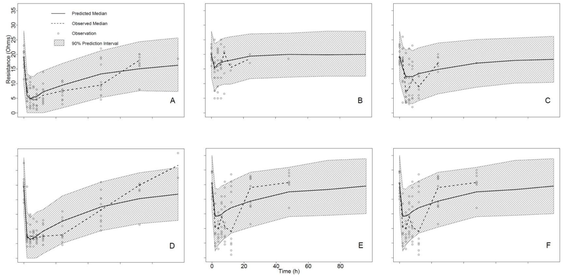


Figure 3: Predictive performance of the population pharmacodynamic model of the anti-platelet effect following oral administration of aspirin (325 mg) (A & D), naproxen (220 mg) alone (B), naproxen (440 mg) alone (E), concomitant administration of aspirin (325 mg) and naproxen (220 mg) (D) and aspirin (325 mg) and naproxen (440 mg) (F).

Model Precision Plots

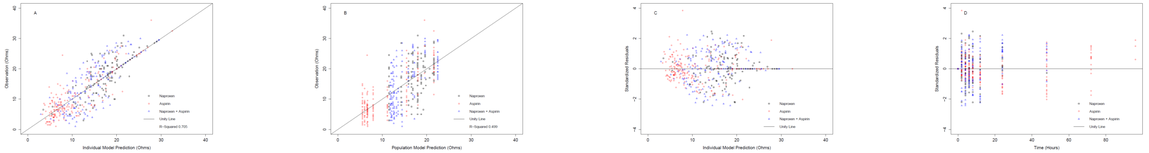


Figure 4: Precision plots of the final population pharmacodynamic model observing (A) individual model prediction versus observed value, (B) population model prediction versus observed value, (C) individual model prediction versus standardized residuals, and (D) observation time versus standardized residuals.

Monte Carlo Simulation

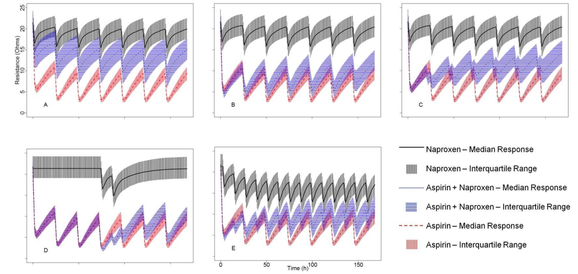


Figure 5: Simulated aggregometry profiles of 1000 theoretical patients after multiple dosing of aspirin (325 mg), naproxen (220 mg) and aspirin/naproxen combination therapy over a week. Simulations include (A) aspirin once daily dosed simultaneously with naproxen, (B) naproxen dosed once daily 3 hours after aspirin, (C) naproxen dosed once daily 3 hours before aspirin, (D) naproxen dosed twice daily for one day (3h and 15h) after aspirin, (E) naproxen dosed twice daily for one week (3h and 15h) after aspirin.

Conclusion

- **A population-based pharmacodynamic model well captured the interaction between aspirin and naproxen on the inhibition of platelet aggregation.**
- **Interaction is moderate as compared to the complete blockage of the aspirin-mediated effect by ibuprofen.**
- **Fast off rate (k_{off}) suggests naproxen remains bound to COX for a decreased amount of time, relative to ibuprofen (Table II).**
- **Simulations of several dosing regimens indicate that co-administration of aspirin before naproxen would have decreased clinical consequences.**
- **Future studies characterizing pharmacokinetics for use in a full PK/PD model may be warranted .**

References

1. Benedek, I.H., et al., *Variability in the pharmacokinetics and pharmacodynamics of low dose aspirin in healthy male volunteers.* J Clin Pharmacol, 1995. **35**(12): p. 1181-6.
2. Calvo, M.V., et al., *Pharmacokinetics of naproxen in healthy volunteers and in patients with diabetic microangiopathy.* Int J Clin Pharmacol Biopharm, 1979. **17**(12): p. 486-91.
3. Hong, Y., et al., *Population pharmacodynamic modelling of aspirin- and ibuprofen-induced inhibition of platelet aggregation in healthy subjects.* Clin Pharmacokinet, 2008. **47**(2): p. 129-37.

Acknowledgements

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