POPULATION PHARMACOKINETICS MODELING OF CLOPIDOGREL IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION (PCI)

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1. Introduction

The objective of this study is to investigate the population pharmacokinetics of **clopidogrel** in patients (n= 132)undergoing percutaneous coronary intervention and receiving different doses of clopidogrel. In order to do that, we collected as many as possible factors that may affect the pharmacokinetics of clopidogrel and modeled them using Monolix® software. Processing the results and comparing with the base model, we can find those factors whose effects are more likely.

2. Methods, Study population:

The study involved 132 cardiovascular patients with Iranian origin hospitalized in Tehran Heart Center, undergoing Precotaneous Coronary Intervention (PCI) and receiving oral clopidogrel treatment. The population included males (26.2%) and females (74.8%) with different ages, weights (76.9±19.4 kg), IBMs (28.6±8.2 kg/m^2), and genotypes (in types I to III with frequency of 67.6, 29.2 and 3.3 percent respectively). They were treated randomly with different doses of clopidogrel (including 75, 150, 300 and 600 mg) at random intervals.

3. Factors considered:

For each person a form containing personal information (sex, height, body weight and age), blood factors (Hemoglobin, Hematocrit, Red blood cells, and serum creatinine), Clopidogrel dosage received and the time of administration, concomitant medications (including Aspirin, ACEIs, ARBs, Beta-blockers, statins and nitrates), last PT and INR number, body activation, genotype, alcohol and cigarette consumption, were filled out.

Frequency tables show that in the population under study, 3% had been drinking alcohol and 29.2% had been smoking before hospitalization. Patients were receiving concomitant drugs including Aspirin (75.7%), ACEIs (49.4%), ARBs (13.1%), statins (69.6%), nitrates (85.8%) and beta-blockers (72.7%). Only 22.2% of them had body activation and their last number of INR= 1.1±0.2 .

4. Pharmacokinetic modeling:

For pharmacokinetics modeling, we used **Monolix v4.3.3 software**. Pharmacokinetics parameters in our one-compartment model included Ka (absorption rate constant) equal to 5.97 h^{-1}, K (elimination rate constant) equal to 0.126 h^{-1}, and V (distribution volume) equal to 21. (www.lixsoft.com. License is provided by Tehran University of Medical Sciences.)

5. Conclusion

In this study we studied 132 PCI patients hospitalized in Iran receiving clopidogrel drug. Using population pharmacokinetics, we found that factors like genotype, alcohol and cigarette consumption, body activation, blood factors like serum creatinine, red blood cells and hemoglobin, and receiving concomitant drugs from ACEIs, nitrates, beta-blockers, statins and Aspirin pills may affect pharmacokinetics of clopidogrel. It is expected that physicians consider these factors while prescribing clopidogrel.

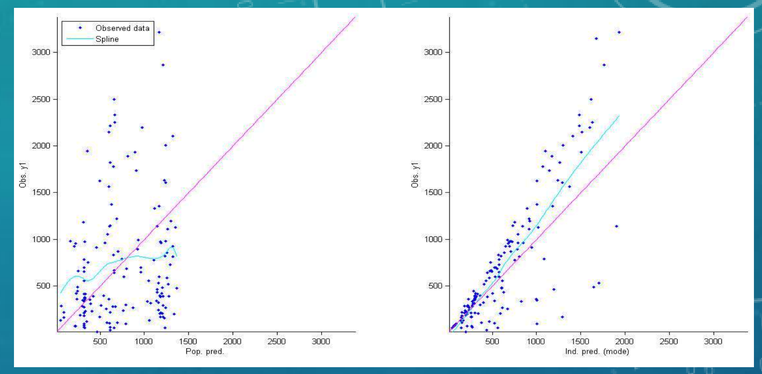

Table 1- Population pharmacokinetic parameters of final base model for clopidogrel calculated by Monolix® software

Parameters	Values	SE	R.S.E%
Ka	5.97	-	-
V	0.303	0.062	20
K	0.0398	0.0089	22
Omega_Ka	2.05	180	8840
Omega_V	0.603	0.14	24
Omega_K	0.656	0.15	22
B	0.533	0.053	10

Loglikelihood of different covariates effective on Pharmacokinetics of Clopidogrel

Model	Loglikelihood	LLD	p-value	Conclusion
Basic model	2282.19			
Nitrates	2267.60	14.59	>3.84	++
ASA	2269.64	12.55	>3.84	++
2C19	2270.95	11.24	>3.84	++
Hemoglobin	2275.46	6.73	>3.84	+
Cigarette	2276.20	5.99	>3.84	+
Alcohol	2276.37	5.82	>3.84	+
RBC	2276.90	5.29	>3.84	+
Creatinine	2277.25	4.94	>3.84	+
statin	2277.45	4.74	>3.84	+
ACEI	2277.57	4.62	>3.84	+
Beta-b	2278.10	4.09	>3.84	+