GENETIC FACTORS IN EFFICIENT DRUG USE

The Importance of Genetic Differences Among Individuals in Drug Use

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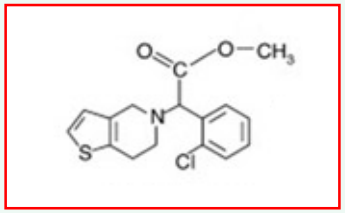
WHY is there a difference in EFFICACY between individuals in drug treatment?

WHY is there a differences in SIDE EFFECTS between individuals who take the same medicine?

PLAVİX® TABLET 75 mg

Clopidogrel



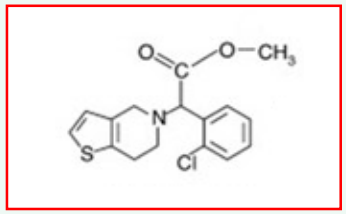
WHY is there a difference in EFFICACY between individuals in drug treatment

Summary of Product Characteristic

4.1. Therapeutic indications

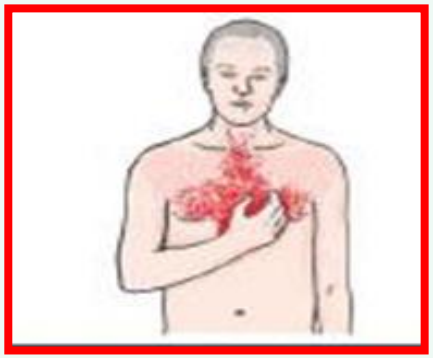
Prevention of atherothrombotic events:

- **Adult patients: Previous Myocardial Infarction, Previous Stroke or Peripheral Arterial Disease**
- **Adult patients: Acute Coronary Syndrome**
- **Prevention of atherothrombotic and thromboembolic events in atrial fibrillation**



CYP2C19 → **2-oxo-clopidogrel** → **inhibitor of platelet aggregation.**

An increased risk of major adverse cardiovascular development (MI, stent thrombosis) in individuals with the *CYP2C19* * *2* allele.



1. Name of the medicinal product

Plavix 300 mg film-coated tablets

2. Qualitative and quantitative composition

Plavix 75 mg film-coated tablets

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

4. Clinical particulars

4.1 Therapeutic indications

Secondary prevention of atherothrombotic events

Clopidogrel is indicated in:

• Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

• Adult patients suffering from acute coronary syndrome:

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

4.4 Special warnings and precautions for use

Cytochrome P450 2C19 (***CYP2C19***)

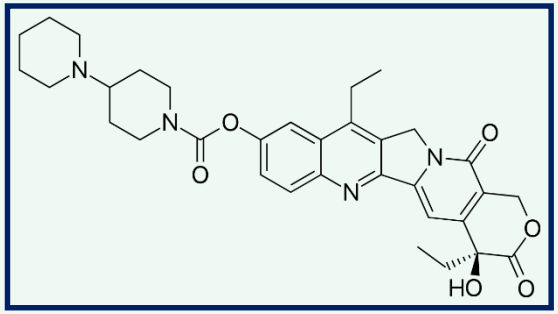
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

The effectiveness of drugs used in some diseases

Therapeutic area	Efficay rate (%)
Analgesics (COX-2 inhibitors)	80
Depression (SSRIs)	62
Cardiac arrhythmia	60
Schizophrenia	60
Alzheimer	30
Oncology	25

WHY is there a differences in SIDE EFFECTS between individuals who take the same medicine?

Irinotecan



Approximately 35% of patients receiving irinotecan experience ADRs such as severe diarrhea and neutropenia.

1. Name of the medicinal product

CAMPTO 20 mg/ml concentrate for solution for infusion

Irinotecan is indicated for the treatment of patients with advanced colorectal cancer

Patients with Reduced UGT1A1 Activity:

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan to inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals.

Patients known to be homozygous for *UGT1A1*28* should be administered the normally indicated irinotecan starting dose.

In the USA, adverse drug reactions are 6.7% in hospital-treated patients, and about 100,000 of these have caused death (Lazarou et al .; JAMA, 1998).

It is estimated that adverse drug reactions in the USA result in spending $ 100 billion.

Biological Factors

Age
Gender
Disease
Pregnancy
GENETICS

Pharmaceutical

Drug dose
Frequeny of administration
Pharmaceutic formulation
Routes of administration

Absorption

Pharmacokinetics

Systemic circulation

Distribution
Metabolism
Excretion

Site of action

Pharmacodynamics

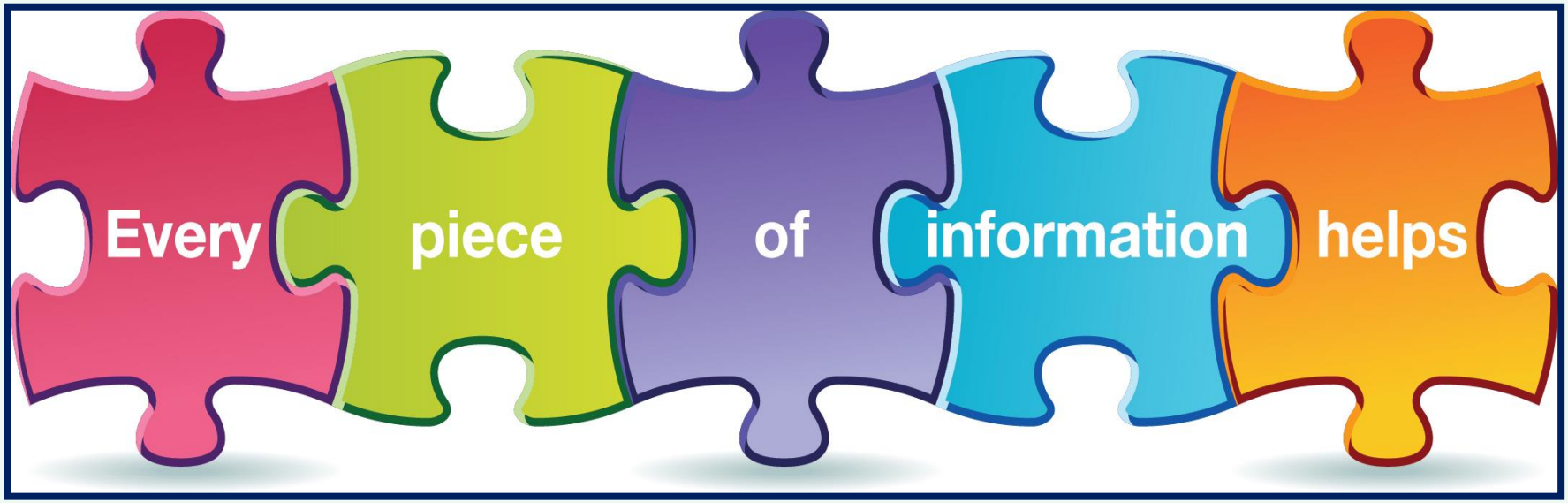
EFFECTS

Culturel factors

Patient's attitude
Patient involvement

Environmental factor

Drugs
Foods
Tobacco smoking
Alcohol
Environmental pollutants
Climate



Biological factors
Age, Gender, Race
Pregnancy, Body size,
Renal/hepatic function,
Existing diseases,
Medication compliance,
Gastric pH,
etc.

Drug-related factors
Drug structure and conformation,
Dosage scheme,
Half-life time,
Bioavailability,
Administration route,
Therp. ratio.

Environmental fac.
Diet / Nutrients,
Smoking/alcohol consumption/ coffee intake,
Co-delivered drugs and drug interactions.

GENETIC FACTORS

Genetic variations in
DRUG
related pathways

PHARMACOGENETICS: Pharmacogenomics investigate the genetic basis of inter-individual differences in drug responses, and adverse events.

PHARMACOGENOMICS: The area that investigates the genome function on the activity of drugs.

Pharmacogenetic objectives:

To maximize drug effectiveness,

To minimize the toxicity that may occur,

Drug selection according to the genetic structure of the person,

Dose selection according to the genetic structure of the person.

Absorbtion
Distribution
Metabolism
Excretion

Drug targets
Disease related pathways

Pharmacokinetics + Pharmacodynamic → Drug response
Side Effect

Drug Metabolised Enzymes
Drug transporters

Receptors
Ion channels
Lipoproteins
Coagulation factors

Pharmaco-Toxicogenetic marker	DRUG	Test Purpose
Test-MANDATORY		
EGFR Express.	Cetuximab	Efficacy
HER2/NEU over express.	Trastuzumab	Efficacy
CCR-5-tropic HIV-1	Maraviroc	Efficacy
Philadelphia Chr.-positive	Dasatinib	Efficacy
Test-RECOMMEND		
*HLA-B*1502*	Carbamazepine	Safety
*HLA-B*5701*	Abacavir	Safety
CYP2C9	Warfarin	Safety
VKORC1	Warfarin	Safety
Protein C defciency	Warfarin	Safety
TPMT polymorp.	Azathioprine, mercaptopurine, thioguanine	Safety Safety Safety
UGT1A1 polymorrp.	Irinotecan	Safety
G6PD deficiency	Rasburicase	Safety
Üre cycle disorder	Valproic acid	Safety

Pharmaco-Toxicogenetic marker	DRUG	Test purpose
Only-INFORMATIVE		
c-KIT expression	Imatinib	Efficacy
CYP2C19 polymorp.	Voriconazole	Safety
CYP2C9 poliymorp.	Celecoxib	Safety
CYP2D6 polymorp.	Atomoxetine,	Eff & Safety
	tamoxifen,	Eff & Safety
	voriconazole	Eff & Safety
DPD deficiency	Capecitabine,	Safety
	fluorouracil	Safety
EGFR ekspresyon	Erlotinib	Efficacy
G6PD deficiency	Rasburicase, primaquine	
NAT polymorp	Isoniazid,	Safety
	rifampin	Safety
Philadelphia chromosome negative	Busulfan	Efficacy
PML/RAR gene expression	Tretinoin	Safety

Drugs that have contraindication as a pharmacogenetic (FG) biomarker in their use

Drug	Group	Gene	FG Inform.
Abacavir	Infection	*HLA-B*	*HLA-B*5701* carriers
Capecitebine	Oncology	*DPYD*	*DPD* deficiency
Fluorouracil	Dermatology	*DPYD*	*DPD* deficiency
Pegloticase	Rheumotogy	*G6PD*	*G6PD* deficiency
Pimozide	Psychiatry	*CYP2D6*	*CYP2D6* slow metabolisors
Quinine sulfate	Infection	*G6PD*	*G6PD* deficiency
Rasbucirase	Oncology	*G6PD*	*G6PD* deficiency
Thioridazine	Psychiatry	*CYP2D6*	*CYP2D6* slow metabolisors