PK.gen

sefh
Sociedad Española de Farmacia Hospitalaria

Clínica Universidad de Navarra

Practical considerations on TDM

Azucena Aldaz
Pharm D, Ph D.

ACPE EAHP Academy Seminar 2018
An ACPE application based activity

eahp
european association of hospital pharmacists

in collaboration with Roger Jelliffe, founder of LAPK (University of Southern California)

CONFLICT OF INTEREST

There are no conflicts of interest to declare

in collaboration with Roger Jelliffe, founder of LAPK (University of Southern California)

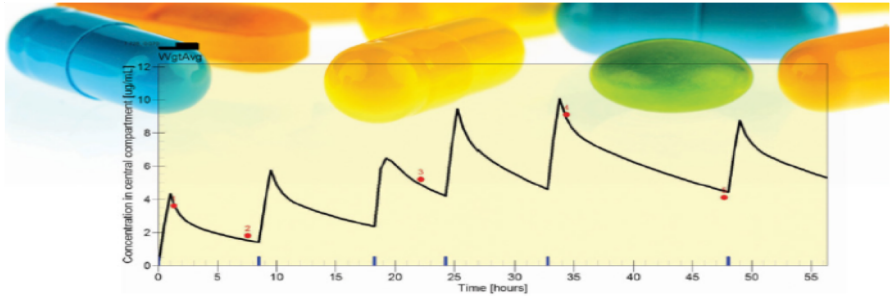
Outline

- The Therapeutic Drug Monitoring Process
- Request form
- Laboratory measurement
- Pharmacogenetics-guided TDM
- Overview of commonly monitored drugs

Therapeutic drug monitoring process

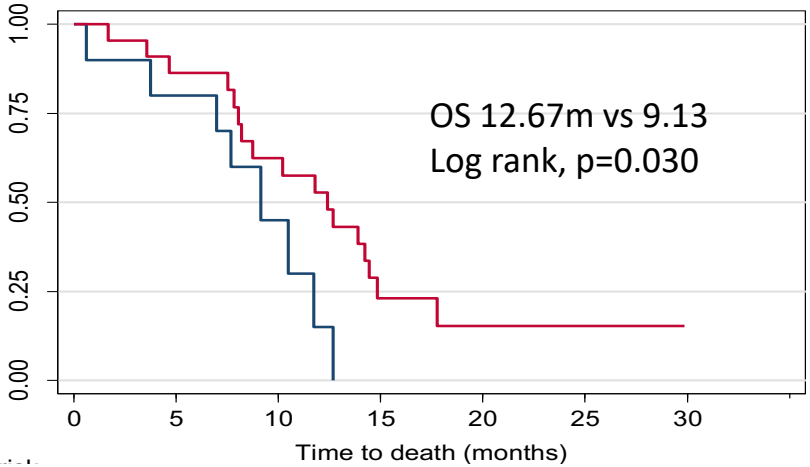
GOAL

Improve health outcomes in a cost-effective manner, by optimizing individual pharmacotherapy

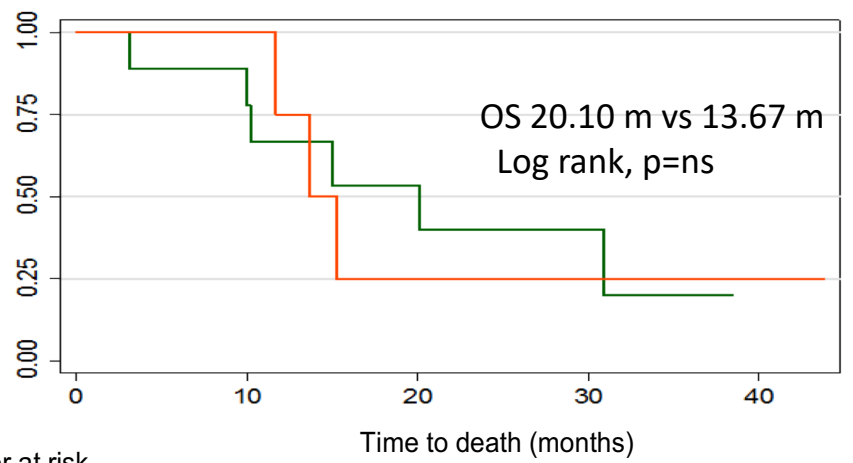


Clinical Outcomes in Pancreas Cancer

Metastatic



Locally Advanced



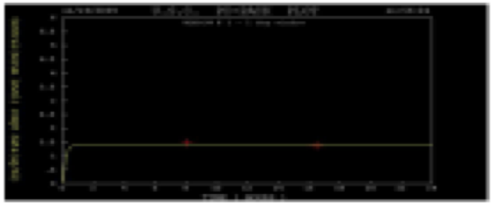
Number at risk

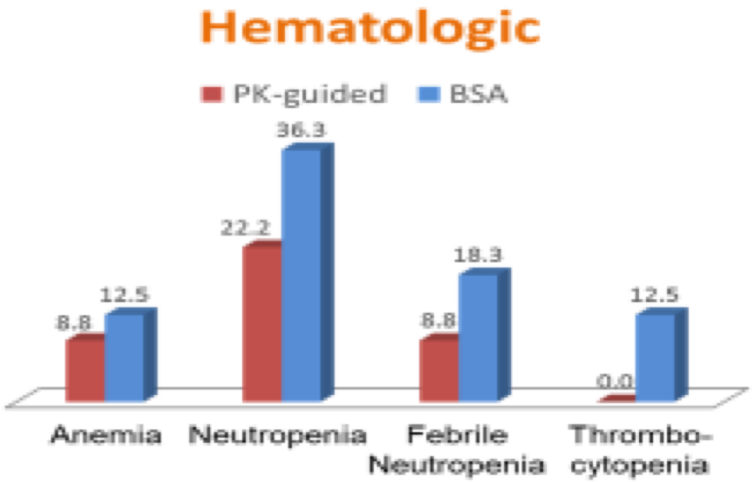
PK-guided dose	9	7	4	2	0
BSA dose	5	4	1	1	1

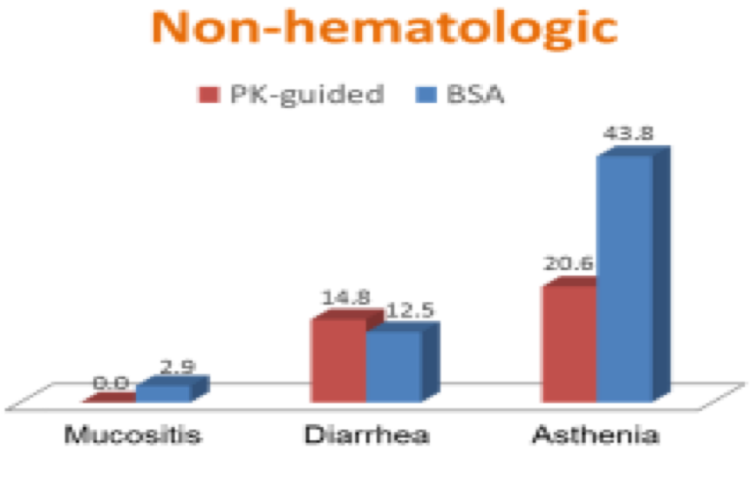
BSA dose PK-guided dose

PK guided dose BSA dose

Authors: Azucena Aldaz et al, 2017







Neutropenia and asthenia, the most common adverse events, were significantly lower in the PK-guided group

HOW???

Tools

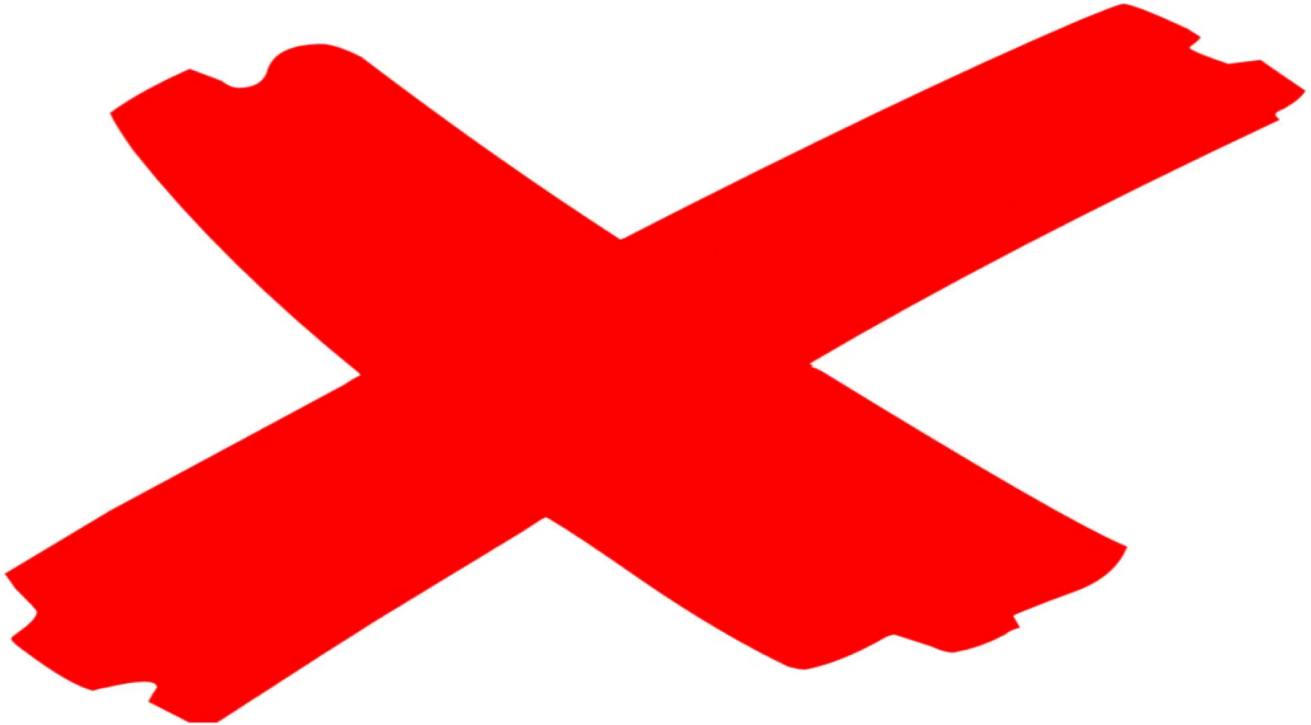
Knowledge

Therapeutic drug monitoring process

- Monitoring request
- Assessment of request suitability
- Biological samples: optimal sampling strategies
- Concentration data: Bioanalytical methods for TDM
- Estimation of individual pharmacokinetics parameters
- Analysis of clinical information
- Pharmacokinetic report

Learning Objectives

- Learn the different phases of the TDM process
- Know the advantages and disadvantages of the different analytical methods
- Understand the importance of quantifying concentrations below LLOQ
- Determine the assay error
- Assess the Bayesian adjustment methods

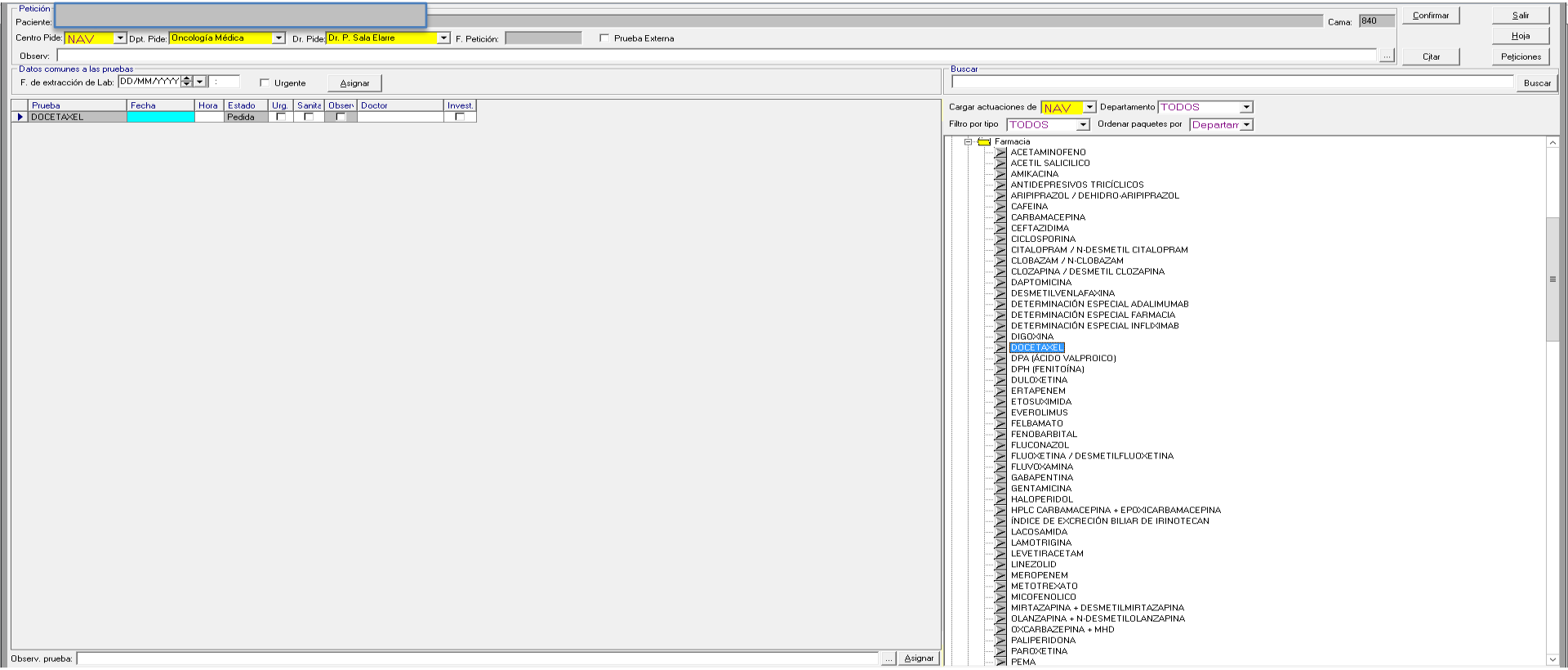


- Co-medication

Figure 1 The six components of a Health Information System

HIS
Health Information System

Nowadays, professionals directly access in the electronic patient record to the drug monitoring application included by the Clinical Pharmacokinetic Unit in the HIS (Health Information System) of the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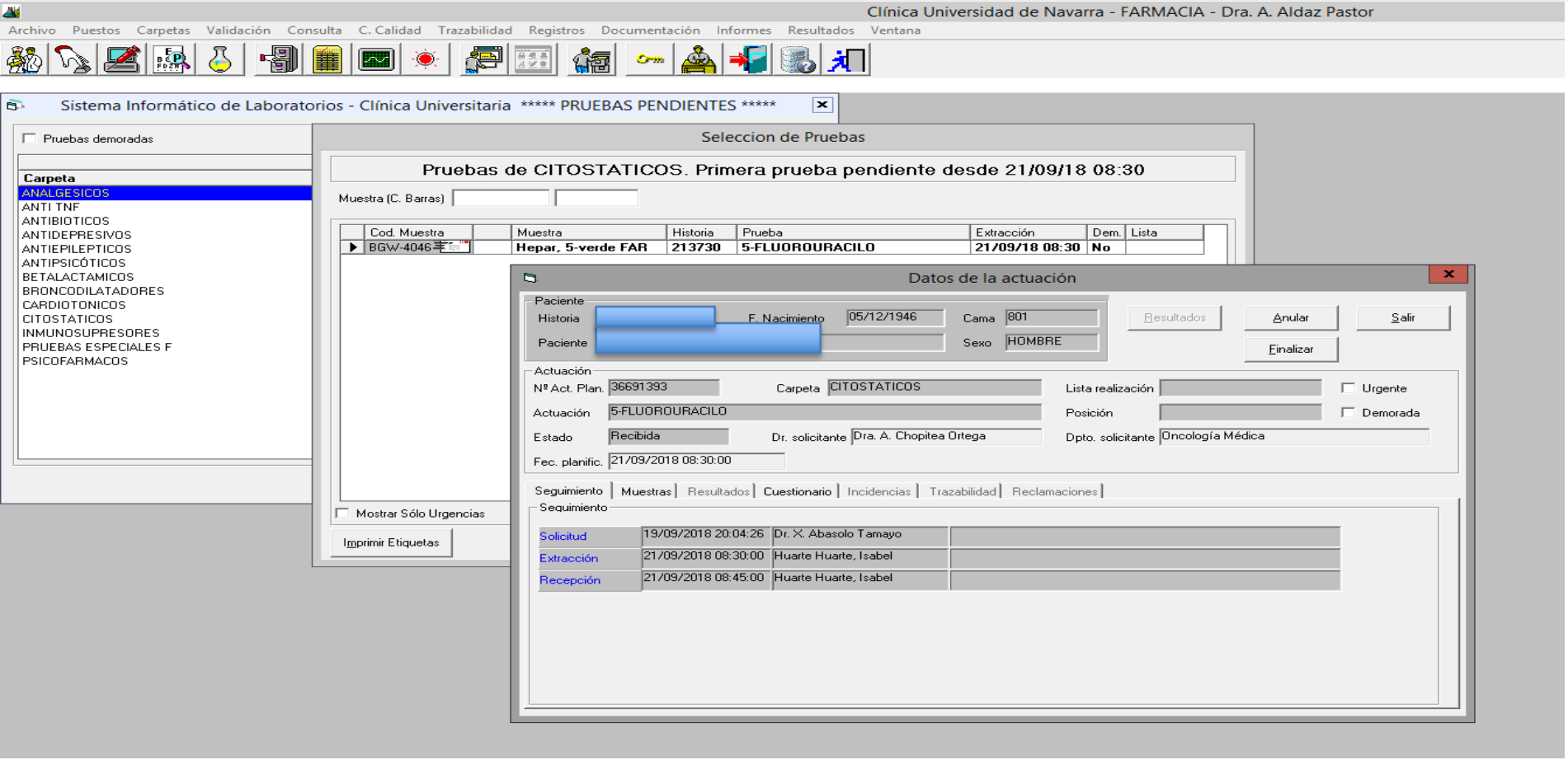
Paciente:
Cama: 840
Confirmar
Salir
Centro Pide: NAV
Dpt. Pide: Oncología Médica
Dr. Pide: Dr. P. Sala Elarre
F. Petición:
Prueba Externa
Hoja
Observ:
Citar
Peticiones
Datos comunes a las pruebas
F. de extracción de Lab: DD/MM/YYYY
Urgente
Asignar
Buscar
Buscar
Prueba
Fecha
Hora
Estado
Urg.
Sanita
Observ
Doctor
Invest.
DOCETAXEL
Pedida
Cargar actuaciones de NAV
Departamento TODOS
Filtro por tipo TODOS
Ordenar paquetes por Departam
Farmacia
ACETAMINOFENO
ACETIL SALICILICO
AMIKACINA
ANTIDEPRESIVOS TRICÍCLICOS
ARIPIPRAZOL / DEHIDRO-ARIPIPRAZOL
CAFEINA
CARBAMACEPINA
CEFTAZIDIMA
CICLOSPORINA
CITALOPRAM / N-DESMETIL CITALOPRAM
CLOBAZAM / N-CLOBAZAM
CLOZAPINA / DESMETIL CLOZAPINA
DAPTOMICINA
DESMETILVENLAFAXINA
DETERMINACIÓN ESPECIAL ADALIMUMAB
DETERMINACIÓN ESPECIAL FARMACIA
DETERMINACIÓN ESPECIAL INFLIXIMAB
DIGOXINA
DOCETAXEL
DPA (ÁCIDO VALPROICO)
DPH (FENITOÍNA)
DULOXETINA
ERTAPENEM
ETOSUXIMIDA
EVEROLIMUS
FELBAMATO
FENOBARBITAL
FLUCONAZOL
FLUOXETINA / DESMETILFLUOXETINA
FLUVOXAMINA
GABAPENTINA
GENTAMICINA
HALOPERIDOL
HPLC CARBAMACEPINA + EPOXICARBAMACEPINA
ÍNDICE DE EXCRECIÓN BILIAR DE IRINOTECAN
LACOSAMIDA
LAMOTRIGINA
LEVETIRACETAM
LINEZOLID
MEROPENEM
METOTREXATO
MICOFENOLICO
MIRTAZAPINA + DESMETILMIRTAZAPINA
OLANZAPINA + N-DESMETILOLANZAPINA
OXCARBAZEPINA + MHD
PALIPERIDONA
PAROXETINA
PEMA
Observ. prueba:
Asignar


Clínica Universidad de Navarra - FARMACIA - Dra. A. Aldaz Pastor
Archivo Puestos Carpetas Validación Consulta C. Calidad Trazabilidad Registros Documentación Informes Resultados Ventana
Sistema Informático de Laboratorios - Clínica Universitaria ***** PRUEBAS PENDIENTES *****
Pruebas demoradas
Carpeta
ANALGESICOS
ANTI TNF
ANTIBIOTICOS
ANTIDEPRESIVOS
ANTIEPILEPTICOS
ANTIPSICÓTICOS
BETALACTAMICOS
BRONCODILATADORES
CARDIOTONICOS
CITOSTATICOS
INMUNOSUPRESORES
PRUEBAS ESPECIALES F
PSICOFARMACOS
Seleccion de Pruebas
Pruebas de CITOSTATICOS. Primera prueba pendiente desde 21/09/18 08:30
Muestra (C. Barras)
Cod. Muestra
Muestra
Historia
Prueba
Extracción
Dem.
Lista
BGW-4046
Hepar, 5-verde FAR
213730
5-FLUOROURACILO
21/09/18 08:30
No
Mostrar Sólo Urgencias
Imprimir Etiquetas
Datos de la actuación
Paciente
Historia
F. Nacimiento
05/12/1946
Cama
801
Paciente
Sexo
HOMBRE
Resultados
Anular
Salir
Finalizar
Actuación
Nº Act. Plan.
36691393
Carpeta
CITOSTATICOS
Lista realización
Urgente
Actuación
5-FLUOROURACILO
Posición
Demorada
Estado
Recibida
Dr. solicitante
Dra. A. Chopitea Ortega
Dpto. solicitante
Oncología Médica
Fec. planific.
21/09/2018 08:30:00
Seguimiento
Muestras
Resultados
Cuestionario
Incidencias
Trazabilidad
Reclamaciones
Seguimiento
Solicitud
19/09/2018 20:04:26
Dr. X. Abasolo Tamayo
Extracción
21/09/2018 08:30:00
Huarte Huarte, Isabel
Recepción
21/09/2018 08:45:00
Huarte Huarte, Isabel

Datos
Paciente: DIG. NAV

Procesos-Asistencia | Intervenciones | Informes | Pruebas | Diagnósticos | Fotografías/Videos | Historia digital | Evolución | Prescripción | Infecciones

Opciones
Responsable/Asistencia Asistencia/Responsable

- Asistencias
- Sin asistencia
- 29/08/18 - 19/09/18
  - Oncología Médica (Dr. P. Sala Elarre) P/B Firmado electrónicamente
- 29/08/18 - 29/08/18
- 20/08/18 - 20/08/18
- 12/08/18 - 14/08/18
- 19/06/18 - 19/06/18
- 04/06/18 - 04/06/18
- 28/05/18 - 28/05/18
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- 20/03/17 - 24/03/17
- 26/02/17 - 27/02/17
- 22/02/17 - 24/02/17
- 15/02/17 - 20/02/17
- 15/02/17 - 15/02/17
- 09/02/17 - 09/02/17
- 06/02/17 - 06/02/17

Opciones
Ver analítica Ver canceladas

Prueba	Dpto.	Fecha	Estado	Citado para	Realizada por	Firmado por
Ecocardiograma-Doppler^	Cardiología-H...	17/09/18 16:17	Inf. electr...	Ecocardiografo 2	Dra. I. Díaz Dorronsoro	Dra. I. Díaz Dorron...
Lactato deshidrogenasa (LDH)	Lab. Bioquími...	17/09/18 08:39	Informada			
Fosfatasa alcalina	Lab. Bioquími...	17/09/18 08:39	Informada			
Creatinina sangre	Lab. Bioquími...	17/09/18 08:39	Informada			
Urea sangre	Lab. Bioquími...	17/09/18 08:39	Informada			
Ionograma sangre	Lab. Bioquími...	17/09/18 08:39	Informada			
Bilirrubina	Lab. Bioquími...	17/09/18 08:39	Informada			
gamma-Glutamiltransferasa (GGT)	Lab. Bioquími...	17/09/18 08:39	Informada			
Alanina aminotransferasa (ALT)	Lab. Bioquími...	17/09/18 08:39	Informada			
Aspartato aminotransferasa (AST)	Lab. Bioquími...	17/09/18 08:39	Informada			
CO2 sangre	Lab. Bioquími...	17/09/18 08:39	Informada			
Drenaje con Ecog.(Colocación C...	Radiología	15/09/18 19:21	Inf. electr...	ECOGRAFO Nº 2	Dra. M. R. García de Eulat...	Dra. M. R. García d.
TTPA	Lab. Hematol...	15/09/18 13:25	Informada			
Fibrinógeno	Lab. Hematol...	15/09/18 13:25	Informada			
T. Protrombina	Lab. Hematol...	15/09/18 13:25	Informada			
Serie Abdomen Agudo^	Radiología	14/09/18 23:18	Inf. electr...	RX PUESTO Nº2	Dr. A. Benito Boillos, Dr. A. ...	Dr. A. Benito Boillos
5-FLUOROURACILO	Farmacia	14/09/18 20:01	Realizada			
CO2 sangre	Lab. Bioquími...	14/09/18 08:51	Informada			
Ionograma sangre	Lab. Bioquími...	14/09/18 08:51	Informada			
5-FLUOROURACILO	Farmacia	14/09/18 08:30	Realizada			
Creatinina sangre	Lab. Bioquími...	13/09/18 08:40	Informada			
CO2 sangre	Lab. Bioquími...	13/09/18 08:40	Informada			
Ionograma sangre	Lab. Bioquími...	13/09/18 08:40	Informada			
Aspartato aminotransferasa (AST)	Lab. Bioquími...	13/09/18 08:40	Informada			
gamma-Glutamiltransferasa (GGT)	Lab. Bioquími...	13/09/18 08:40	Informada			
Bilirrubina	Lab. Bioquími...	13/09/18 08:40	Informada			
Fosfatasa alcalina	Lab. Bioquími...	13/09/18 08:40	Informada			
Lactato deshidrogenasa (LDH)	Lab. Bioquími...	13/09/18 08:40	Informada			
Alanina aminotransferasa (ALT)	Lab. Bioquími...	13/09/18 08:40	Informada			
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Ionograma sangre	Lab. Bioquími...	12/09/18 08:42	Informada			
Hemograma	Lab. Hematol...	12/09/18 08:42	Informada			
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Creatinina sangre	Lab. Bioquími...	11/09/18 08:37	Informada			
CO2 sangre	Lab. Bioquími...	11/09/18 08:37	Informada			
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Hemograma	Lab. Hematol...	08/09/18 08:41	Informada			
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Urea sangre	Lab. Bioquími...	06/09/18 08:28	Informada			
Ionograma sangre	Lab. Bioquími...	06/09/18 08:28	Informada			
CO2 sangre	Lab. Bioquími...	06/09/18 08:28	Informada			
Ionograma sangre	Lab. Bioquími...	05/09/18 08:59	Informada			
CO2 sangre	Lab. Bioquími...	05/09/18 08:59	Informada			
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Fosfatasa alcalina	Lab. Bioquími...	04/09/18 08:36	Informada			

504258/2018215270 CONTROL 26/09/2018

Paciente: [redacted]
Lista realización: 4754653
F. Nac.: 23/07/1954

Dpto. solicitante: MAD - Digestivo
Doctor solicitante [redacted]

Determinación especial Farmacología

RESULTADOS

Concentración
Informe

MUESTRAS

BGW-8746 25/09/2018 8:09:00

OBSERVACIONES

* PETICIÓN: 13684211
Motivo pet. prueba: niveles de depakine

* CUESTIONARIO:
Nombre de la prueba a realizar: niveles de depakine
Especímen, cantidad y condiciones de conservación: 300 mg 1-1-1
Persona de contacto del departamento solicitante: [redacted]

Prediction of Future Serum Concentrations with Bayesian Fitted Pharmacokinetic Models: Results with Data Collected by Nurses Versus Trained Pharmacy Residents

Therapeutic Drug Monitoring
16:166–173 © 1994 Raven Press, Ltd., New York

B. Charpiat, *V. Breant, †C. Pivot-Dumarest, ‡P. Maire, and §R. Jelliffe

TABLE 1. *Patient demographic data for the RCD and NCD groups*[a]

	RCD group	NCD group
Male	3 (30%)	7 (30.4%)
Female	7 (70%)	16 (69.6%)
Age (yr)	79.1 ± 7.9	81.3 ± 7
Height (m)	1.6 ± 0.15	1.6 ± 0.08
Weight (kg)	58.8 ± 14.4	60.5 ± 12.6
Initial estimated creatinine clearance (ml/mm/1.73 m^2)	41.9 ± 15.6	42.5 ± 15
No. of patients with four levels in first cluster	10[b]	6[b]
No. patients with ≤three levels in first cluster	0[b]	17[b]
All doses given i.m.	3	4
All doses given i.v.	6	13

[a] All ± data are listed as mean values ± SD.
[b] $\chi^2 = 12.7$, $p < 0.001$.

TABLE 4. *Percent of serum levels accurately predicted (within ±20%) in RCD and NCD groups using the MAP Bayesian one-compartment fitted model*

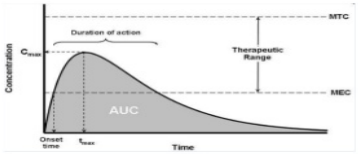
B1	RCD	NCD	*p*-value[a]
PSLAP	80%	22%	<0.01
TSLAP	30%	13%	NS[b]

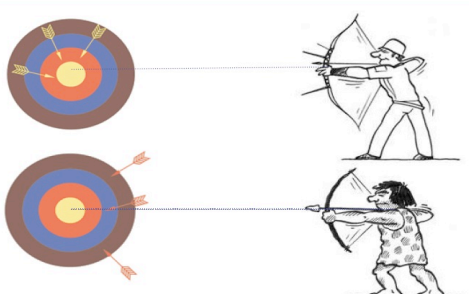
PSLAP = peak levels accurately predicted and TSLAP = trough levels accurately predicted.
[a] Comparing groups.
[b] NS = not significant.

RCD: resident- collected data
NCD: nurse-collected data

Bioanalytical methods for TDM

The most precise methods for dosage adjustment use drug concentrations measured in biological samples, drawn at determined times





We need analytical assays

simple

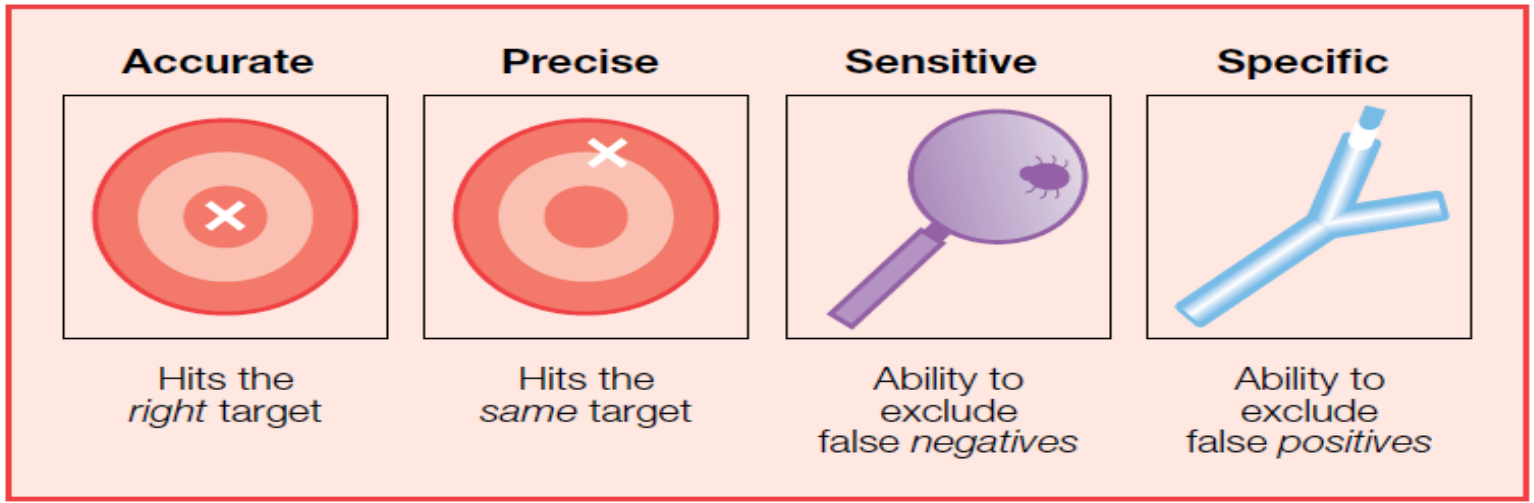
specific

accurate

fast

precise

We need to control the results

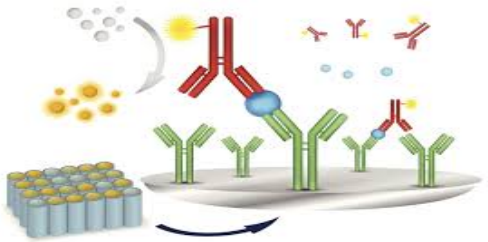

Accurate
Precise
Sensitive
Specific
Hits the *right* target
Hits the *same* target
Ability to exclude false *negatives*
Ability to exclude false *positives*

IMMUNOASSAYS

TDM

CHROMATOGRAPHY

IMMUNOASSAYS



Are bioanalytical methods in which the quantitation of the analyte depends on the reaction of an antigen and an antibody (immune complex)

Homogeneous and Heterogeneous

Competitive and Non-competitive

IMMUNOASSAYS

Reagents

Antibodies

Monoclonal
Polyclonal

Signal-generating labels

- Radioactive atoms
- Enzimes
- Fluorescens probes
- Chemiluminiscens
- Metal
- Liposomes

Separation matrices

Charcoal
Polyethilene glicol
Second antibody
Microbeads
Microwell plate

Chemiluminescent Magnetic Immunoassay—CMIA

???

???

Electrochemiluminescence Immunoassay- ECLIA

???

Fluorescence Polarization Immunoassay - FPIA

Microparticle Enzyme Immunoassay - MEIA

Antibody-conjugated magnetic immunoassay- ACMIA

Quantitative Microparticle System- QMS

Cloned enzyme doner immunoassay- CEDIA

Characterization of cross reactivity by carbamazepine 10,11-epoxide with carbamazepine assays

Sijiu Shen[a], Ronald J. Elin[b], Steven J. Soldin[c,d,*]

ization immunoassay. The cross-reactivity of the epoxide

Measurement of carbamazepine and carbamazepine 10, 11-epoxide by different analytical systems

Systems	Z01*			Z02*			Differ (Z02-Z01)	T value	P value
	N	Mean	STD	N	Mean	STD			
Abbott axsym	1512	7.24	0.26	1514	8.34	0.30	1.10	107.77	<0.001
Abbott TDX/TDXFLX	230	7.28	0.36	233	8.32	0.39	1.04	29.81	<0.001
BDI opus/plus/magnum	22	10.69	0.57	23	11.55	0.62	0.86	4.84	<0.001
Beckman synchron RGT	324	6.31	0.47	325	6.69	0.48	0.38	10.19	<0.001
Cedia	136	8.41	0.41	137	8.74	0.39	0.33	6.81	<0.001
Chiron ACS:180	42	6.51	0.52	41	6.70	0.52	0.19	1.66	0.100
Dade ACA	299	7.75	0.29	299	9.96	0.44	2.21	72.52	<0.001
Dade dimension	356	7.03	0.33	359	11.71	0.63	4.68	124.27	<0.001
Roche cobas integra	116	7.89	0.34	117	8.41	0.36	0.52	11.33	<0.001
Syva emit	11	7.83	0.73	11	7.85	0.81	0.02	0.06	0.952
Syva emit 2000	59	7.44	0.50	59	7.37	0.45	−0.07	0.80	0.426
Technicon immuno-1	68	7.32	0.80	68	7.4	0.76	0.08	0.60	0.551
Vitros	110	5.14	0.41	109	5.14	0.42	0.00	0.00	1.000
All methods	3339	7.21	0.74	3349	8.56	1.53	1.35	45.91	<0.001

* The target value for Z01 is 7.5 mg/L carbamazepine, for Z02 is 7.5 mg/L carbamazepine plus 5.0 mg/L carbamazepine 10, 11-epoxide. The mean concentrations are given in mg/L. Student's t test is used for statistical analysis.

S.J. Soldin et al. / Clinical Biochemistry 34 (2001) 157–158

Estimation of Carbamazepine and Carbamazepine-10,11-Epoxide Concentrations in Plasma Using Mathematical Equations Generated With Two Carbamazepine Immunoassays

Gwendolyn A. McMillin, PhD,[1,2] JoEtta M. Juenke, MT(ASCP),[1] Gertie Tso, MT(ASCP),[3] and Amitava Dasgupta, PhD[4]

Cross-Reactivity of Carbamazepine-10,11-Epoxide With the PETINIA, ADVIA Centaur, and CEDIA*

Epoxide (µg/mL)	PETINIA	ADVIA Centaur	CEDIA
0.0	ND (—)	ND (—)	ND (—)
1.0	0.96 (96.0)	ND (—)	ND (—)
1.5	1.3 (86.6)	ND (—)	ND (—)
2.5	2.3 (92.0)	ND (—)	ND (—)
3.5	3.7 (105.7)	ND (—)	ND (—)
5.5	5.4 (98.2)	0.37 (6.8)	0.52 (9.4)
7.5	7.3 (97.3)	0.47 (6.3)	0.62 (8.2)
10.0	10.3 (103.0)	0.64 (6.4)	1.27 (12.7)
18.0	16.8 (93.3)	0.97 (5.3)	2.09 (11.6)
25.0	23.4 (93.6)	1.92 (7.7)	2.65 (10.6)

Immunoassays

Automated

Standarized methods

Low sample volume

No sample preparation (or minimum)

Less time of analysis

Fairly low cost (instruments, reagents)

Easy to use. Personal minimally qualified

Less sensitivity (heterogeneous > homogeneous)

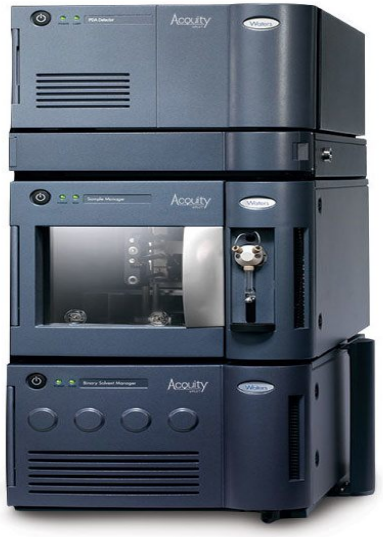
Less specificity

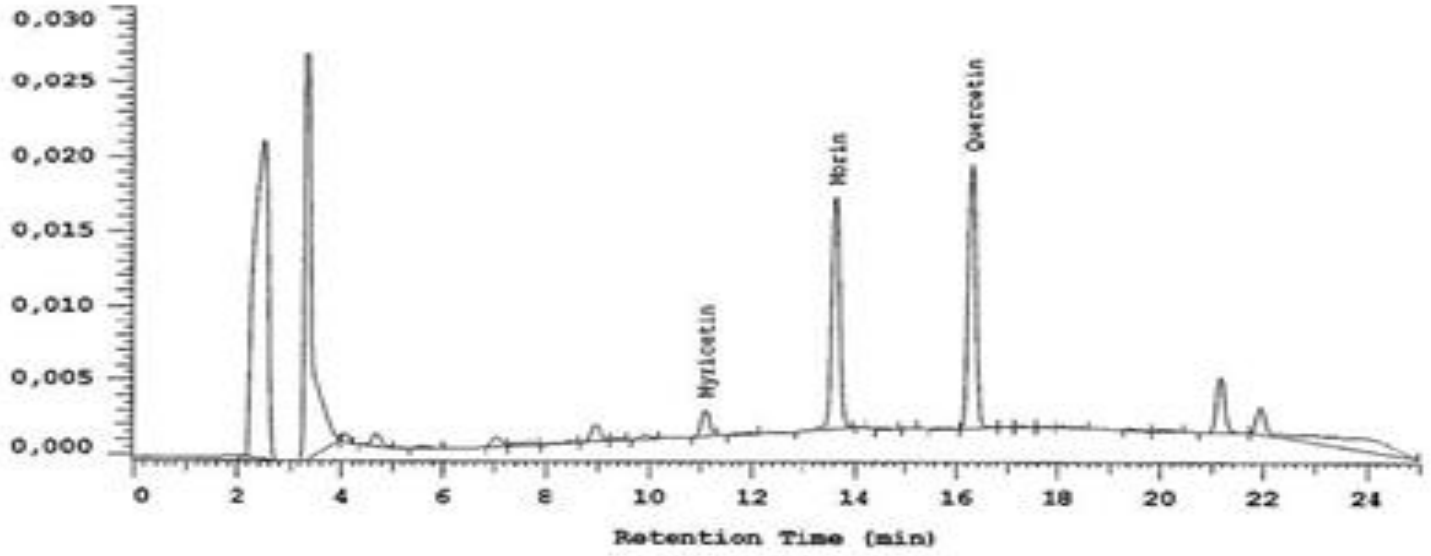
Total dependence on provider

Limited supply of assays

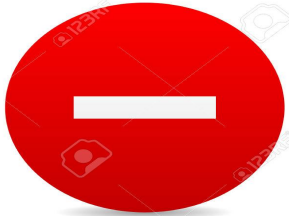
No availability for new drugs

Chromatography




0,030
0,025
0,020
0,015
0,010
0,005
0,000
Myricetin
Morin
Quercetin
0
2
4
6
8
10
12
14
16
18
20
22
24
Retention Time (min)

Chromatographic methods



Standarized and in-house methods

Good or high sensitivity (LC-MS/MS)

Good or high specificity (LC-MS/MS)

HPLC high sample volume required

Sample preparation required

Lengthy analysis (HPLC)

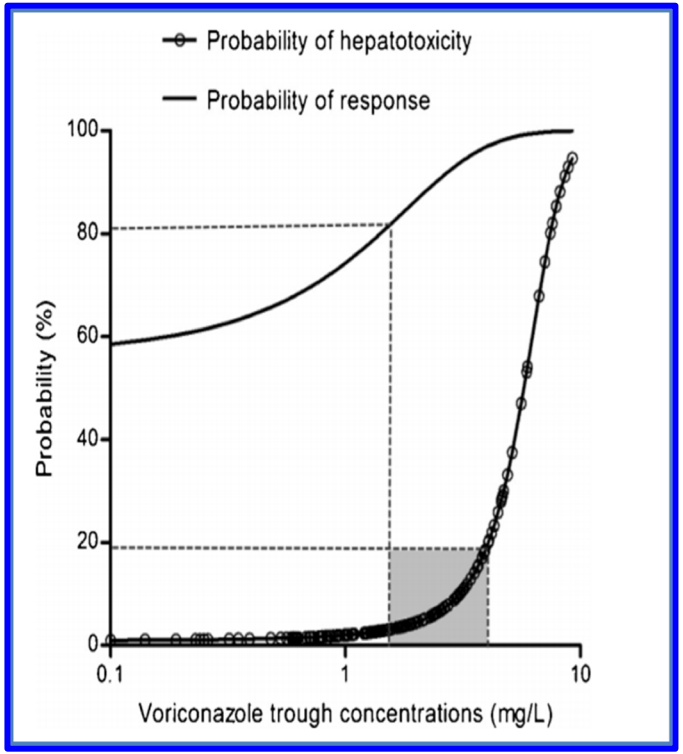
Moderate analysis length (LC-MS/MS)

Expensive instrumentation

Qualified and experienced staff

Which drugs may require therapeutic drug monitoring?

- Narrow and established target concentration range
- Significant interindividual pharmacokinetic variability
- No high intraindividual pharmacokinetic variability
- A better relationship between concentration and response that between dose and response
- Therapeutic benefit demonstrate by TDM
- Possibility of having analytical methods to quantify the drug



Methods of dosage optimization

Methods “a priori”

Based on population pharmacokinetics parameters

Methods “a posteriori”

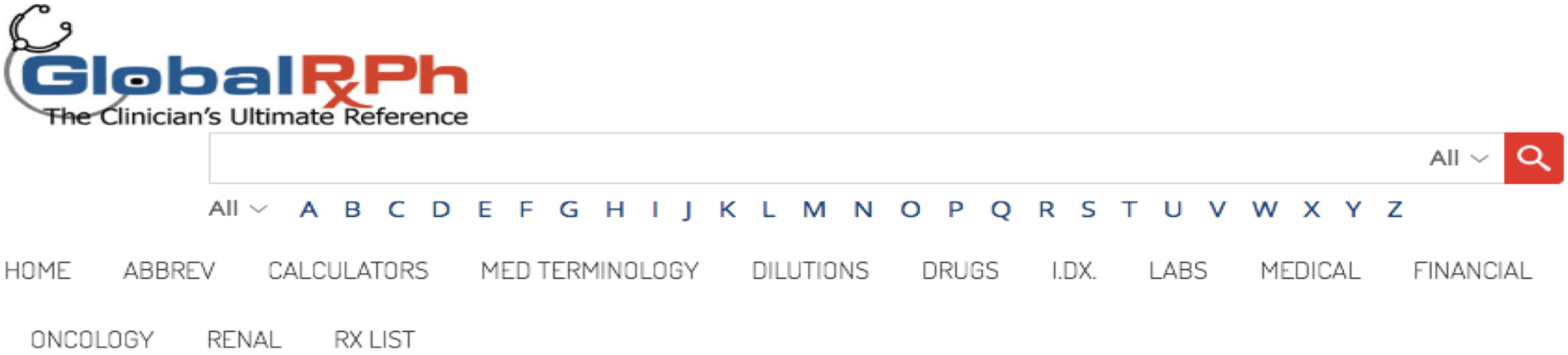
Regression methods

Use data of TDM concentrations

Bayesian methods

Use population pharmacokinetics parameters + data of TDM concentrations

Methods “a priori”



PHARMACOKINETIC DOSING

AMINOGLYCOSIDE-VANCOMYCIN DOSING

<< Link to other Dosing Calculators / Internal Medicine >> NEW

Patient Name: Location: Conventional dosing

Select drug:
- Gentamicin
- Tobramycin
- Amikacin
- Vancomycin

Program Hints -

Need dosing information for once daily dosing?

Gent-tobra: Mild (4 mg/kg)/ Amikacin (10 mg/kg)

Age: Weight: Kg Gender: Male

SCR: Height: Centimeters

Desired peak: Desired trough: Infusion time: 0.5 hours

Volume of distribution: Please Select Value L/kg

Usual range: aminoglycosides: 0.25 - 0.35 Vancomycin: 0.65 - 0.9

Algorithms

(example Lithium)

$$\text{Dose} = 6.21\ C^{ss}_{goal} - 1.93_{form} - 2.84\ \text{ADT} - 0.07\ \text{age} + 1.88\ \text{sex} + 0.08\ \text{weight} + 5.14$$

N = 100 patients with bipolar disorder

These methods have limited utility and should only be used for initial dosing, provided that the population information on which they are based is well known and validated in routine clinical practice.

Methods “a posteriori”

Linear regression

$$y = a.x + b \Rightarrow \ln Cp = \ln(D/Vd) - Ke.t$$

$$a = Ke = \frac{\sum(t).\sum(\ln Cp) - n\sum(t.\ln Cp)}{\left(\sum(t)\right)^2 - n\sum(t^2)}$$

$$b = \ln\frac{D}{Vd} = \frac{\sum(t).\sum(t.\ln Cp) - n\sum(t^2)\sum(\ln Cp)}{\left(\sum(t)\right)^2 - n\sum(t^2)}$$

Advantages of linear regression

- Simplicity
- Speed
- No computer is needed

Limitations

- Implicit errors in linearization
- Does not allow the use of all information

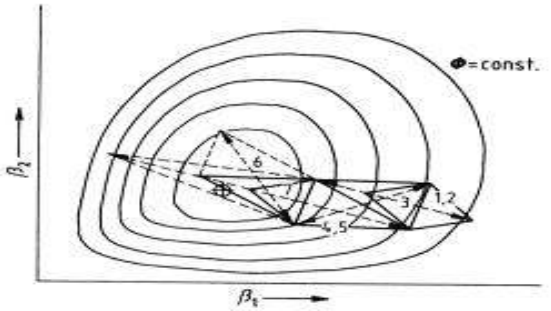
Methods “a posteriori”

Non- Linear regression

$$SS = \sum_{i=1}^{n} Wi.(Ci,t - f(Pm,t))^2$$

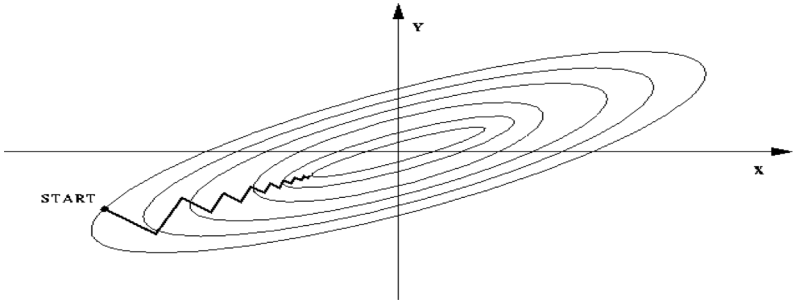
Direct search algorithms

Simplex
Nelder-Mead



Gradient algorithms

Steepest Descent
Marquart-Levenberg
Gauss-Newton



Advantages of Non- linear regression

- Data weighting
- Use of complex equations, including kinetic and clinical parameters
- Does not require additional population information

Limitations

- Need a greater number of concentrations (≥3)
- Need a computer
- Requires experience to detect false solutions

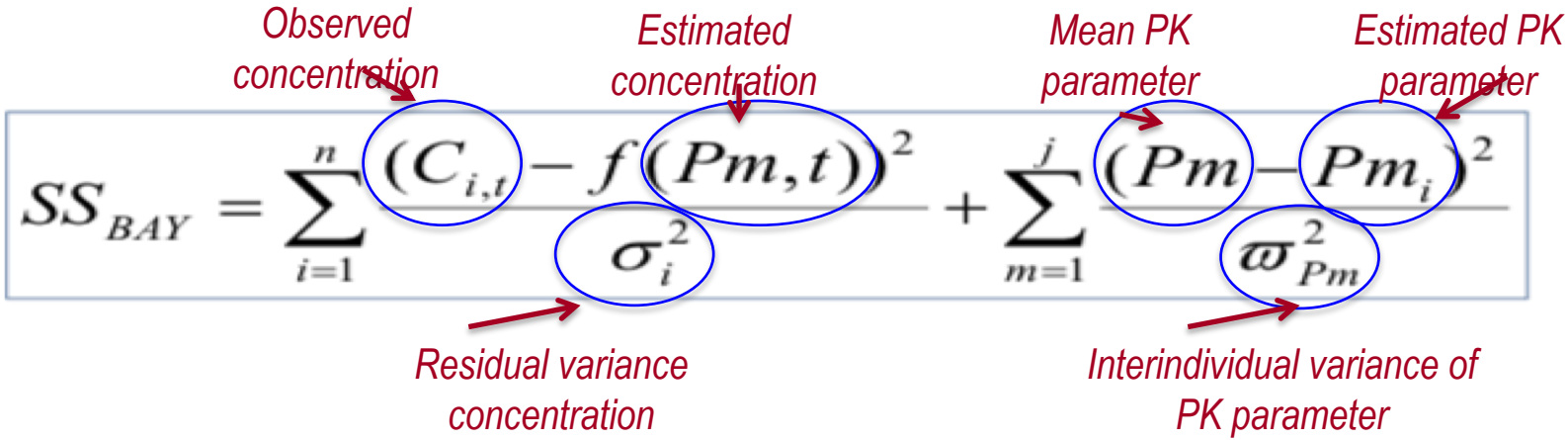
Bayesian methods

Bayes' theorem, is used in many different ways.

In TDM, it provides a way to revise existing predictions or probabilities given new or additional evidence, using either parametric or (better) nonparametric approaches

$$P(A|B) = \frac{P(B|A)\,P(A)}{P(B)}$$

Thomas Bayes
1702 - 1761



Information “a priori”:

PK parameters
Interindividual variance of each PK parameter
Residual variance of concentrations

Current information:

Observed concentrations

Information “a posteriori”:

Estimated PK bayesian parameters
Estimated concentrations using PK bayesian parameters

Advantages of Bayesian methods

- Minimum experimental information
- Flexibility of sampling time
- Consistent results
- Application to different PK models

Limitations

- Clinical training
- Validate the PK model in the own population

All estimation methods require a total control of :

- time of administration
- time of the previous doses or at least of the usual schedule in the case of ambulatory patients

How to do Optimal TDM and Individualize Drug Therapy Optimally

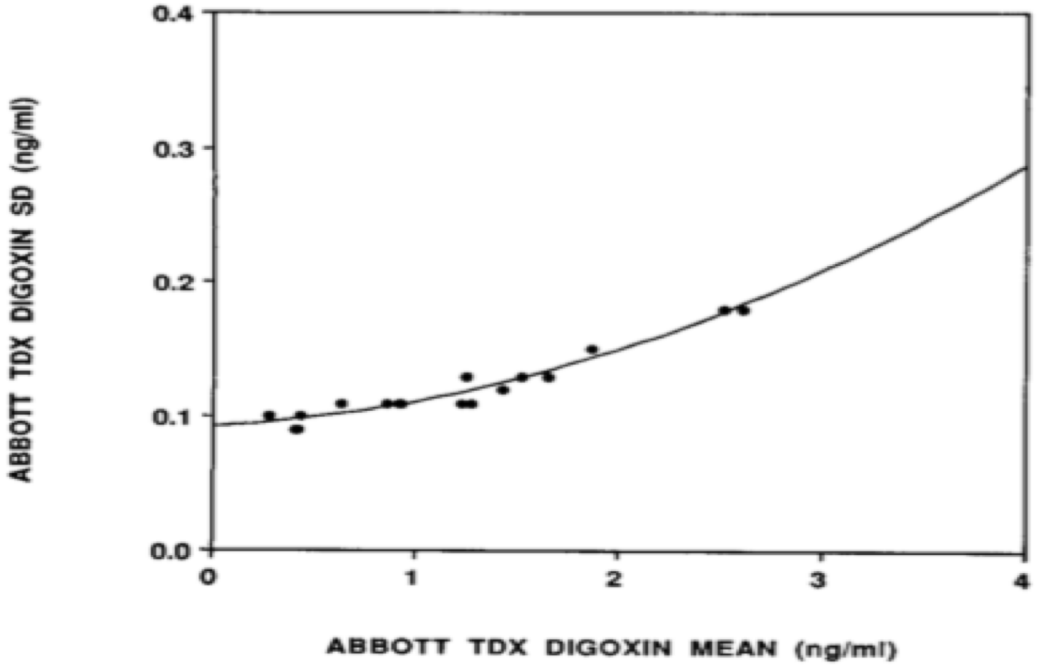
We need good data, **accurately recorded**, precisely measured, with a good quantitative ***index*** of its **credibility**.

1 - WHEN was it drawn? Look at the clock on the wall, or your watch. Record the time as military time, to the minute, from 0000 to 2359 hrs. This is MOST IMPORTANT!

Same for the doses – even more important.

2 – How CREDIBLE is the assay?

We need to know the assay error over the entire range of the assay, down to and including the zero blank



Assay Error Pattern

Not all data have equal credibility.

There have been various empirical weighting schemes such as:

- unity weighting
- weighting by the reciprocal of the measured concentration (or of its squared value)
- the use of a constant coefficient of variation
- and others.

We need to know the relative amount of information contained in a data point, to give more quantitative importance to one that is known with good precision and less to one known with less precision (greater measurement error).
Use 1/variance (Fisher information) as the correct error description

Fisher Information quantifies the credibility of a lab measurement

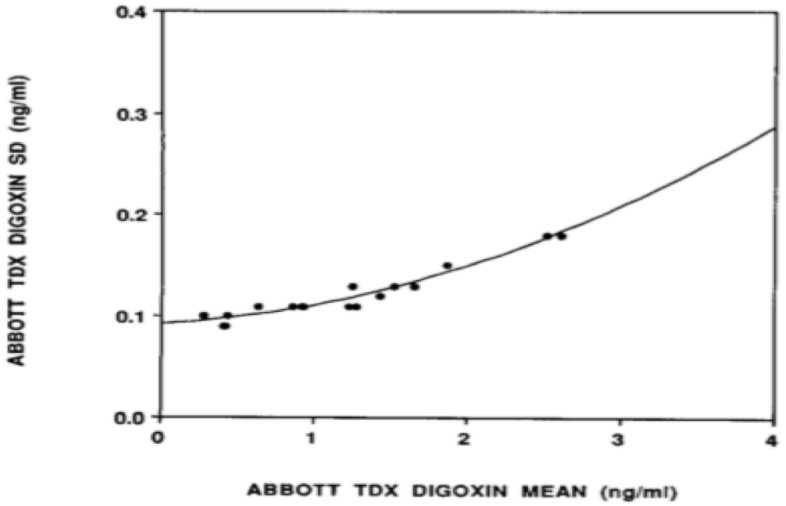
- Fisher Information = 1/Variance
- So need to know, or have a good estimate, of the SD of every serum level.
- Labs always get SD anyway, to get the CV%.
- Then, Variance = SD^2
- And Credibility = Fisher info = 1/Var.

Assay CV% versus correct weight, Fisher Info

- Assume, for example, 10% assay CV
- If conc = 10, SD = 1, var = 1, weight = 1
- If conc = 20, SD = 2, var = 4, weight = ¼ - Aha!
- So a constant linear % error (the assay CV%) is NOT the correct measure of credibility!
- As conc approaches zero, CV% approaches infinity.
- But assay SD, var, weight are always finite. Fisher info is the correct measure of assay precision.
- Also, no need for LLOQ any more!

Determining the Assay SD polynomial

- Measure blank, low, medium, high, and very high samples in at least quintuplicate.
- Get mean conc + SD for each sample.
- Fit a polynomial to the mean and SD data.
- $SD = A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3$
- Then can weight each single measurement by the reciprocal of its variance (Fisher Info)
- No lower detectable limit (LOD) or limit of quantification (LOQ)!
- No need to censor (withhold) any data.



Different weighting schemes lead to different parameter values being found in fitted pharmacokinetic models

This is well known, and has been explicitly shown in pharmacokinetic studies

Therapeutic Drug Monitoring
16:552–559 © 1994 Raven Press, Ltd., New York

Population Pharmacokinetic Models: Effect of Explicit Versus Assumed Constant Serum Concentration Assay Error Patterns upon Parameter Values of Gentamicin in Infants on and off Extracorporeal Membrane Oxygenation

*†Warren F. Dodge, ¶Roger W. Jelliffe, ‡Joseph B. Zwischenberger, ‖Renee A. Bellanger, §James A. Hokanson, and *†Wayne R. Snodgrass

$$SD\ (\mu g/ml) = 0.170455 - (0.043038\ C) + (0.017003\ C^2)$$

Polynomial equation

$$SD\ (\mu g/ml) = A + (0.00\ C) + (0.00\ C^2)$$

A = Constant SD of 0.5 ug/ml

The two population models differ only in the laboratory assay SD pattern used.

IQR (interquartile range) = 75th percentile − 25th percentile = central 50th percentile of values. DF50 = the dispersion factor covering the central 50% of the distributions found = (75th percentile − 25th percentile) divided by 1.32.

[a] An assay SD error pattern that assumes a constant SD of 0.5 μg/ml at all serum gentamicin concentrations.

[b] The explicitly determined laboratory assay SD error pattern.

TABLE 2. *Gentamicin pharmacokinetic parameter values (V_d and K_{el}) for 11 neonates undergoing extracorporeal membrane oxygenation*

	Constant assay SD error pattern[a]	Explicit assay SD error pattern[b]
V_d (L/kg)		
Mean	0.602	0.813
SD	0.053	0.253
25th	0.551	0.609
50th	0.602	0.696
75th	0.602	0.875
IQR	0.051	0.266
DF50	0.039	0.202
K_{el} (h^{-1})		
Mean	0.105	0.084
SD	0.026	0.012
25th	0.086	0.069
50th	0.096	0.075
75th	0.119	0.093
IQR	0.033	0.024
DF50	0.025	0.018

TABLE 4. *Performance evaluation of two gentamicin population models for neonates undergoing extracorporeal membrane oxygenation*

	Predictor[a]	
	Explicit assay SD pattern and median pharmacokientic parameter values	Constant assay SD error pattern and median pharmacokinetic parameter values
Precision		
Mean squared error (MSE)	1.296 (0.786, 1.806)	1.404 (0.855, 1.951)
Root mean squared error (RMSE)	1.138 (0.886, 1.343)	1.185 (0.925, 1.397)
Relative to each other (ΔMSE for predictor explicit weighting minus predictor general weighting)	−0.107 (−0.249, 0.033)	
Bias		
Mean error (ME)	−0.369 (−0.583, −0.607)	−0.645 (−0.843, −0.447)
Relative to each other (ΔME for predictor explicit weighting minus predictor general weighting)	0.276 (0.124, 0.338)	

The two models differ only in the laboratory assay SD error pattern used (explicit assay SD error pattern and assumed constant assay SD error pattern) with median pharmacokinetic parameter values.

[a] Values given are point estimates (95th confidence interval).

Report

The pharmacokinetic report should be written in simple, clear language, avoiding the use of complicated pharmacokinetic terms for clinicians

It should include:

- Patient data
- Drug data
- Concentration data
- Interpretation and comments

DIGOXINA

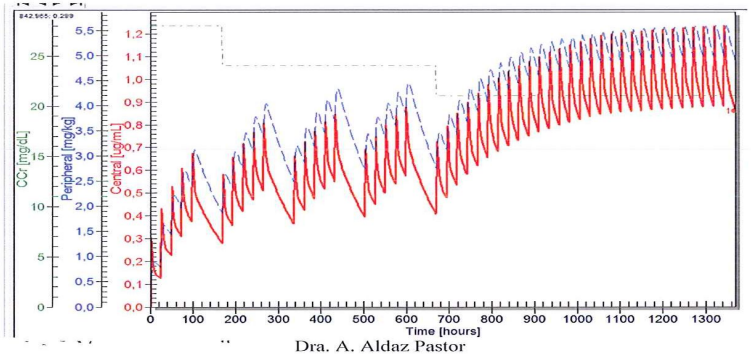
618368

DIGOXINA

Solicita:	Cirugía Cardiaca	Dr. G. Rábago Juan Aracil	11/09/18
Realiza:	Farmacia		18/09/18
Referencia:			

La concentración sérica de digoxina en la muestra obtenida a las 08:36 h del 18/09/18 ha sido de 0,86 ng/mL.
En el gráfico adjunto se muestra el óptimo ajuste de la concentración sérica medida con la simulación realizada en función de la pauta seguida y la evolución renal y ponderal de la paciente. El punto rojo representa la concentración medida.
Se han representado 4 semanas de la antigua pauta de 0,125 mg diario excepto dos días semanales y la actual pauta diaria (0,125 mg diario de Digoxina® comprimidos).

La disfunción renal reduce significativamente el volumen de distribución aparente de digoxina reduciendo su unión a tejido y en la paciente la concentración máxima en miocardio que es la asociada con la respuesta es próxima a 5,5 mcg/kg tejido, que es el mínimo terapéutico.



Dra. A. Aldaz Pastor
Nº colegiado:3031 Nº colegiado·

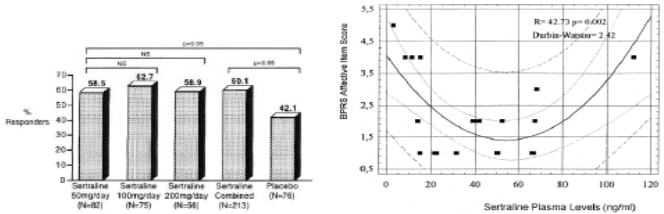
SERTRALINA

Sertralina

Solicita:	Psiquiatría y Psicología Médica	Dr. P. Molero Santos	486	26/02/18
Realiza:	Farmacia	Dra. A. Aldaz Pastor		27/02/18
Referencia:	AAP/aap			28/02/2018

La concentración sérica de sertralina (SER) y su metabolito activo N-sertralina (N-SER) en la muestra obtenida a las 8 h del 27/2/18 han sido, respectivamente, de 158,6 ng/mL y 157,4 ng/mL, siendo la relación N-SER/SER de 0,99.
La pauta que recibe la paciente, desde al menos su ingreso el día 16/2/18, es de 200 mg en el desayuno (Aremis®).

Ya se ha comentado en los informes de otros pacientes los trabajos de Mauri et al sobre la naturaleza curvilínea de la relación entre la concentración de sertralina y la respuesta clínica. En sus trabajos este grupo muestra que los mejores resultados se observan entre 50 y 70 ng/mL. Además, ya en 1995 Preskorn, de cuyo trabajo se muestra una imagen en este informe) advertía sobre el mejor balance beneficio/riesgo de dosis bajas de sertralina sobre dosis más elevadas.
Un aspecto a destacar en los valores medidos es la relación N-SER/SER cuya mediana habitualmente es de 2 y el rango de valores es de 1,7 a 3,4. Sin embargo, en esta paciente es de 0,99. Esto puede reflejar alguna interacción, porque teóricamente han transcurrido ya 10 días desde que se incrementó a la pauta actual y por tanto ya debería haberse alcanzado el estado de equilibrio estacionario en ambas moléculas, aunque no se puede asegurar dada la elevada variabilidad interindividual. Se recomienda valorar la reducción de la dosis actual, al menos a 150 mg en un primer estadio.



Dra. A. Aldaz Pastor
Nº colegiado:929

Can pharmacogenomics be used for posology adjustments?

- Avoid adverse drug reactions (5-fluorouracil, HDMTX)
- Predicts drug efficacy (antineoplastics (RAS, EGFR mutations etc….)
- Predicts drug serum concentrations (Population PK parameters, NEVER individual predictions)
- Can be used to adjust initial posology (Need more tan one variable)

Population Pharmacokinetics and Pharmacogenetics of Imatinib in Children and Adults

Aurélie Petain, Darouna Kattygnarath, Julie Azard, et al.

Clin Cancer Res 2008;14:7102-7109. Published online November 3, 2008.

Purpose: The aim of this study was to explore the effect of several demographic, biological, and pharmacogenetic covariates on the disposition of imatinib and its main metabolite (CGP74588) in both adults and children.

Experimental Design: Thirty-three children with solid malignancies included in a phase II exploratory study and 34 adults with gastrointestinal stromal tumors received 340 mg/m^2 and 400 mg imatinib, respectively. Plasma imatinib and CGP74588 concentrations observed on day 1 and at steady-state were analyzed by a population pharmacokinetic method (NONMEM) to evaluate the effect of age, body weight, age, sex, albuminemia, plasma α1-acid glycoprotein (AGP), and eight polymorphisms corresponding to *ABCB1, ABCG2, CYP3A4, CYP3A5*, and *AGP* (pharmacogenetic data available for 46 of 67 patients).

Results: Analysis of the whole data set in 67 patients showed that apparent clearance (CL/F) of imatinib was positively correlated with body weight and albuminemia and negatively with AGP. By considering these three covariates, the interindividual variability on CL/F decreased from 47% to 19%. The apparent clearance of CGP74588 was similarly dependent on both body weight and AGP and significantly lower (30% reduction) at steady-state. By adding genotype status to the final covariate imatinib model, a 22% reduction in CL/F was observed in heterozygous compared with wild-type patients corresponding to *ABCG2* c.421C>A ($P < 0.05$).

Conclusions: By considering morphologic and biological covariates, a unique covariate model could be used to accurately describe imatinib pharmacokinetics in patients ages 2 to 84 years. Morphologic and biological characteristics have a stronger influence than pharmacogenetics on imatinib pharmacokinetics.

CPIC® Guideline for Fluoropyrimidines and DPYD

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update (October 2017)

Updates since publication:

No updates on dosing recommendations since 2017 publication.

Tables provided in the main manuscript of the guideline:

Table 1. Assignment of likely DPD phenotype based on *DPYD* genotype
Table 2. Recommended dosing of fluoropyrimidines by DPD phenotype

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update (October 2017)

Table 2 Recommended dosing of fluoropyrimidines[a] by DPD phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[b]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

[a]5-fluorouracil or capecitabine. [b]Rating scheme described in Supplement. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

OUR DATA ABOUT PHARMACOKINETICALLY GUIDE 5-FLUOURACIL DOSE-ADJUSTMENT 2016-2017

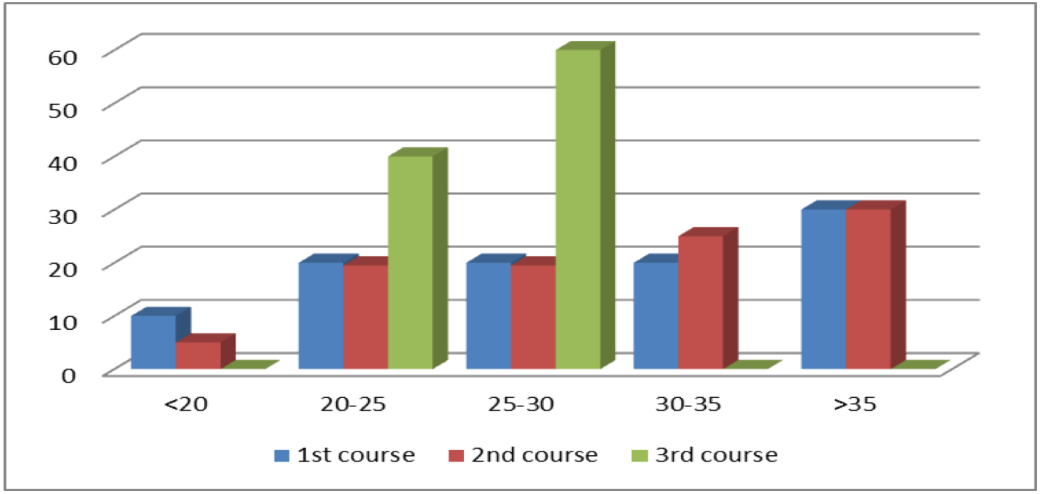
83 courses were monitored

62.6% Dose modificaction

57.7% Increase

42.3% Reduction

Distribution of AUC for 5-FU



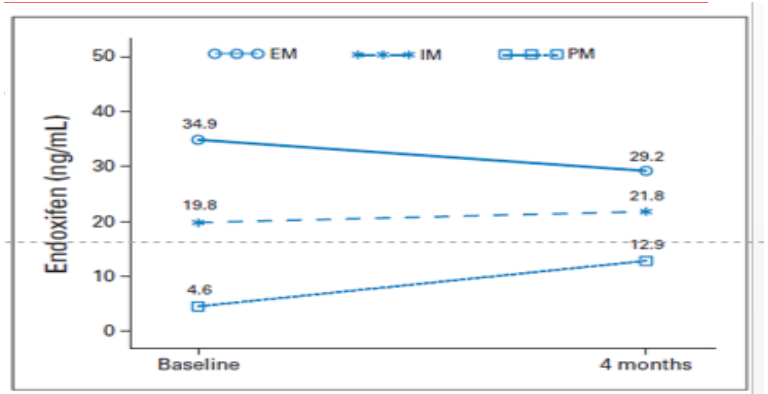
Dose increase (percentage) = 13.75 ± 9.75

Dose reduction (percentage) = 11.71 ± 8.06

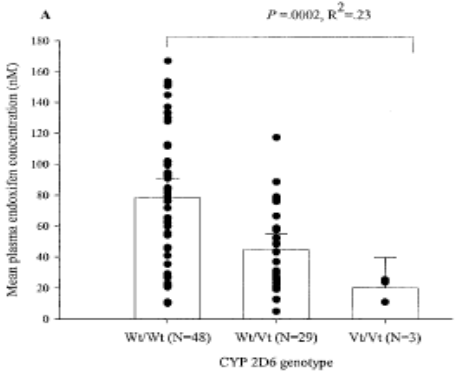
BSA dosing: 30% null-low efficacy

Hypothesis: The CYP2D6 polymorphic state slow metabolizer MAY AFFECT endoxifen plasma concentrations as well as disease-free survival in postmenopausal women ER + under adjuvant treatment with tamoxifen 20mg / day for 5 years

A)



B)



CPIC® Guideline for Tamoxifen based on CYP2D6 genotype

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy (January 2018)

Updates since publication:

No updates on dosing recommendations since publication.

Tables provided in the main manuscript of the guideline:

Table 1. Assignment of likely CYP2D6 phenotypes based on diplotypes
Table 2. Dosing Recommendations for tamoxifen based on CYP2D6 phenotype

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy (January 2018)

Table 1 Assignment of likely CYP2D6 phenotypes based on genotypes

Phenotype[a]		Genotype	Examples of *CYP2D6* diplotypes[b]
Metabolizer	Activity score		
CYP2D6 ultrarapid metabolizer	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 normal metabolizer	1.5 and 2.0	An individual carrying two normal function alleles or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*9, *1/*41, *2/*2,*
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[d]	1.0	An individual carrying two decreased function alleles or one normal function and one no function allele. *An activity score (AS) of 1.0 is associated with decreased tamoxifen metabolism to endoxifen compared to those with an AS of 1.5 or 2.*	**1/*4, *1/*5, *41/*41*
CYP2D6 intermediate metabolizer	0.5	An individual carrying one decreased function and one no function allele	**4/*10,*4/*41, *5/*9*
CYP2D6 poor metabolizer	0	An individual carrying only no functional alleles	**3/*4,*4/*4, *5/*5, *5/*6*

[a]See the *CYP2D6* frequency table[3] for race-specific allele and phenotype frequencies. [b]For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* genotype to phenotype table.[1,6] Note that genotypes with an activity score of 1 are classified as NMs in the online *CYP2D6* genotype to phenotype table. [c]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes. [d]Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. A group of CYP2D6 experts are currently working to standardize the *CYP2D6* genotype to phenotype translation system. CPIC will update the CPIC website accordingly (*CYP2D6* genotype to phenotype table[1,6]).

Therapeutic recommendation[b]	Classification of recommendation[a]
id moderate and strong CYP2D6 inhibitors. Initiate therapy with rec-mended standard of care dosing (tamoxifen 20 mg/day).	Strong
id moderate and strong CYP2D6 inhibitors. Initiate therapy with rec-mended standard of care dosing (tamoxifen 20 mg/day).	Strong
sider hormonal therapy such as an aromatase inhibitor for post-opausal women or aromatase inhibitor along with ovarian function pression in premenopausal women, given that these approaches superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aroma-e inhibitor use is contraindicated, consideration should be given to a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid 2D6 strong to weak inhibitors.	Optional[b]
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ommend alternative hormonal therapy such as an aromatase inhibi-or postmenopausal women or aromatase inhibitor along with ovar-function suppression in premenopausal women given that these roaches are superior to tamoxifen regardless of *CYP2D6* geno-;[43] and based on knowledge that *CYP2D6* poor metabolizers ched from tamoxifen to anastrozole do not have an increased risk currence.[38] Note, higher dose tamoxifen (40 mg/day) increases does not normalize endoxifen concentrations and can be consid-d if there are contraindications to aromatase inhibitor therapy.[45,56]	Strong

normal metabolizer." However, in the case of tamoxifen, prescribing recommendations for those with an s a **10* allele are provided a "moderate" recommendation. In contrast, prescribing recommendations for cause the recommendations are primarily extrapolated from evidence generated from **10* individuals

The remit of this review was narrow and specifically examined the role of CYP2D6. Recent data suggest that the metabolism of TAM is complex and may be related to the effects of more than one genotype. It may be necessary, therefore, for future research to examine other metabolic pathways. In the meantime, further examination of the link between endoxifen levels and clinical outcomes could be of value and could be a mechanism that is easily integrated into existing care pathways.

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notyping for *CYP2D6* for women with breast cancer
ted with tamoxifen

The clinical effectiveness and cost-effectiveness of genotyping for *CYP2D6* for the management of women with breast cancer treated with tamoxifen: a systematic review

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Conclusions

Poor metaboliser plus intermediate metaboliser versus extensive metaboliser

In the four cohorts that explored OS between these groups of patients, there was no evidence of a difference between PMs + IMs and EMs. However, five out of eight cohorts reported significantly improved outcomes for relapse/recurrence in EMs. Interestingly, in one of these cohorts, reported only as an abstract, the significant differences were found only when using the AmpliChip® (Roche Molecular Systems) to genotype for an extensive number of alleles and not when four common alleles were tested for.

Intermediate metaboliser versus extensive metaboliser

There was no evidence of a difference in OS or relapse/recurrence between IMs and EMs from the only cohort that compared outcomes for these two phenotypes.

Poor metaboliser versus extensive metaboliser plus intermediate metaboliser

There was no evidence of a difference in OS or of relapse/recurrence between PMs and EMs + IMs from any of the three cohorts that compared these outcomes in these groups of patients.

Poor metaboliser versus extensive metaboliser

From two cohorts, no evidence of a difference in overall survival (OS) between PMs and EMs was reported. However, there was evidence of improved outcomes in terms of relapse/recurrence (disease-free survival, recurrence-free survival or time to recurrence) in the three cohorts that compared these outcomes.

It has not been possible for this review to ascertain whether pharmacogenetic testing for *CYP2D6* is clinically effective or cost-effective. Key issues include the fact that it is not clear which alleles should be tested for and how phenotypes should then be derived. Assuming we are able to resolve

Drugs subject to monitoring

Antibiotics
PK/PD Index

Antiepileptics
Imprecision in TI

Antidepressants
Curvilineal relationship PK/PD

Anti-cancer drugs:
5-Fluouracil
Irinotecan
Taxanes
Doxorrubicin
MTX
TKI
Monoclonal antibody

Antipsicotics
Curvilineal relationship PK/PD

Immunotherapy
Digestive
Rheumatology
Dermatology

Cardiotonics
Need to control peripheral c.

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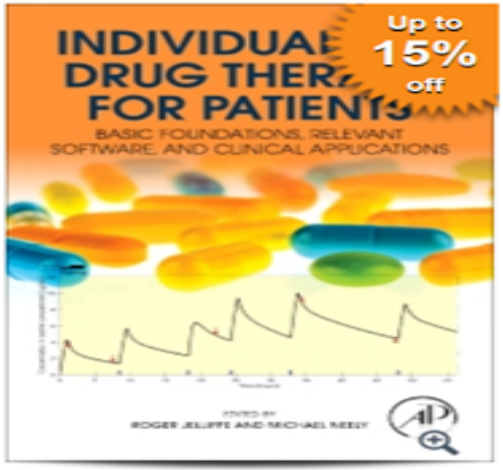
Basic Foundations, Relevant Software and Clinical Applications



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This practical guide provides clinical pharmacologists, pharmacists, and physicians with a valuable resource to help move traditional drug therapy beyond a memorized ritual to being a thoughtful quantitative process aimed at optimizing therapy for each individual patient

If you wish to prescribe drugs to your patients with skill, optimal precision, and consideration for each patient's individual needs, to minimize poor outcomes from blunt, last century one-size-fits-all dosing for the fictitious average patient, consider this book.

More information from Googling "Individualized Drug Therapy" at Elsevier or Amazon.

Take-home messages

- To have good control of every step of the TDM process is necessary for good dosing adjustment of drug therapy in each patient.

- You can´t do drug dosing adjustments if you don´t control all information, and if you don´t use the information correctly.

- Until now, pharmacogenomics has demonstrated a contribution for pharmacodynamic purposes. For dosage optimization, pharmacokinetics is a much more potent tool.


gracias
go raibh maith agat
мерси
mochchakkeram
ngiyabonga
dziękuję
dank je
grazie
teşekkür ederim
kop khun krap
thank you
terima kasih
obrigado
merci
bedankt
danke
dakujem
takk
спасибо
tapadh leat
謝謝
sukriya
sagolun
taiku
arigatô
hvala
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malondo
asante
rahmet
najis tuke
kia ora
mamnun
barka
sobodi
bayarlalaa
chokrane
rahmat
gratias ago
dankie
kam sah hamnida
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gracies
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