Regulatory Consideration in Determining Optimal Dose for Patients

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Start with Dose Response

Not today's discussion, but to have any ability to adjust dose for individuals, you need a good idea of the shape of the D/R Curve.

- Are patients being dosed on the flat part of the curve (ACEI's, ARBs, anti-depressants, many antibiotics) so that small blood level differences will not matter
- Drugs with important toxicity (usually) will require a dose on the steep part of the curve. There, blood level differences in individuals can matter a lot.

Ages of Drug Development – We are in a new (but not that new age)

- Safety: FD&C Act from 1938 to 1962
- Effectiveness - 1962
- Individualization

No change in law led to this age but it is certainly the focus of drug development now:

- Population subsets - Demographic analyses; renal or hepatic disease state/stable
- Pharmacokinetics, PD or pathophysiologic factors that affect outcome, interactions
- Genomic factors and other “enrichments” that affect outcome

Individualization

- What are the main areas of interest with respect to potential causes of individual differences? Broadly, they are:

  PK - differences in how the drug is absorbed, metabolized, excreted. (easy to detect and evaluate)

  PD - differences in the effect of the drug on outcomes: clinical endpoints, biomarkers, surrogates, toxicity.

- We consider both:
  - Group differences: demographic, excretory function
    - Individual differences

The Age of Individualization

No new law or disaster led to this third age (after the age of safety, post-1938, and of effectiveness, post-1962), and it is now in full swing. Better D/R is part of this, but we have been moving swiftly toward closer attention to individual differences

There has been growing recognition that individuals can have significant metabolic differences (some old cases, pseudocholinesterase, acetylation, but striking newer ones, like 2D6 and 2C19 poor metabolizers) and recognition that other drugs being taken can have profound effects on PK. Evaluation of metabolism and drug interactions got a huge boost from a disastrous interaction: terfenadine, an antihistamine causing TdP when metabolism was blocked by 3A4 inhibitors. It has now become routine to examine metabolism and DDI's, as well as the effects of age and gender on PK, to do population PK, and to examine effects of renal and hepatic impairment on PK.

The Age of Individualization

PK differences are easily detected by blood level measurements. Pharmacodynamic differences between people were suspected (doctors pride themselves on individualizing Rx) but relatively few were documented and almost all of our clinical trials look at group, not individual, data, with little ability to look at individual D/R (unless x-over or forced titration, both unusual designs).

Genomics and proteomics change all this, providing an easy measure that can predict major differences in PD, and we're just at the beginning of far more targeted therapy than we've ever imagined

The Age of Individualization

With respect to effectiveness, there are two distinct possibilities

- Individuals can differ in risk of an event (cancer, AMI); major implications for early population selection. Including high risk patients is prognostic enrichment. These patients are likely to have larger absolute effect size.

- Individuals can differ in likelihood of response to a treatment (e.g., because they have a particular receptor – low/high renin levels are a familiar example). Choosing such patients is predictive enrichment, used to target the population for treatment.

Examining Groups

- Before we came to focus on individual differences (genetic, pathophysiologic), the "new age," we began to ask for analyses of effects in demographic subgroups.

Demographic and Other Subsets

History

1983	Elderly Guideline draft
1988	Clin-Stat Guideline focus on subgroups
1989	Elderly Guideline
1993	Gender Guideline
1993	Do not start NDA review unless subset analyses done or readily available
1994	ICH Elderly Guideline; Q & A, 2010
1998	Rule requires subset analyses (21 CFR 314.50), by age, gender and race in ISS, ISE
2012	FDASIA asks for report on whether demographic analyses are being done and communicated

So we now always look for differences in the demographic groups, but there have not been very many M/F, old/young, and B/W difference (some, though).

Problems with Subsets

There is a long history of “subset skepticism” and recognition of the risks of them (Yusuf, Wittes, Peto, Collins) and some famous errors (GISSI finding of effect of SK only in anterior MI and in ISIS-2, aspirin was effective except in patients born under Libra and Gemini). But there is a change in the air and now we do them, cautiously.

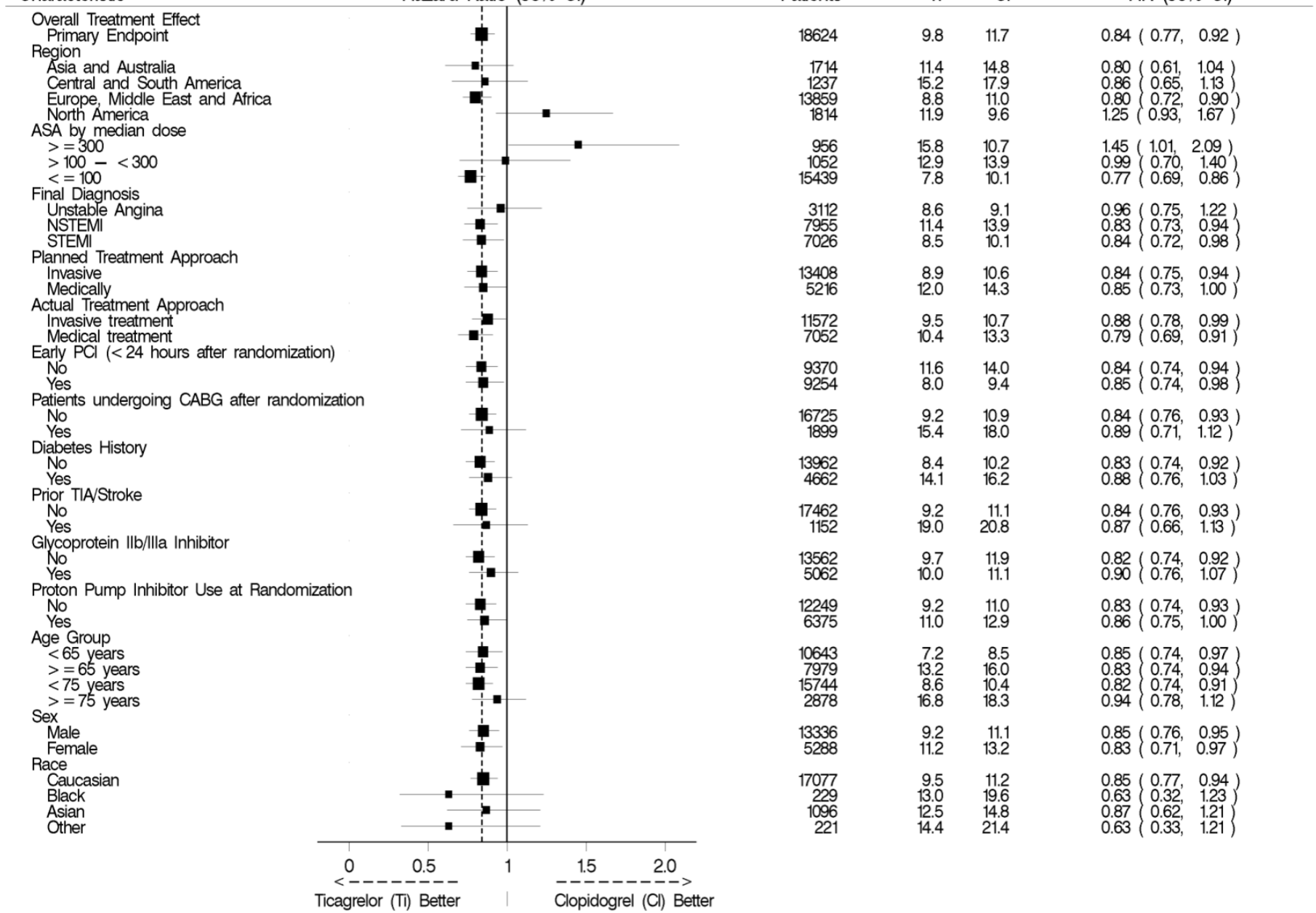
Subset Analyses are the Norm (Cautiously)

Despite awareness of their risks (multiplicity), subset analyses are now routine in journal reports of successful outcome studies (you can't save a failed study by finding a successful subset) presented as so-called "forest plots," a vertical display of hazard ratios and CI's for various population subsets. They are also appearing in labeling (Toprol XL, ticagrelor, dabigatran, apixaban many others). So far, however, not done for symptomatic treatments. Note that not seeing suck difference is also informative.

There has been particular interest in subsets defined by:

- Demographics (Losartan – LIFE)
- Disease severity
- Country/region
- Concomitant treatment – see next slide for ticagrelor data
- Concomitant illness

As the ticagrelor slide suggests, with differences seen both region and aspirin dose, is important to include adjustment for other factors, rather than the single subset analysis.


Characteristic
Hazard Ratio (95% CI)
Total Patients
KM% at Month 12 Ti
KM% at Month 12 Cl
HR (95% CI)
Overall Treatment Effect
Primary Endpoint 18624 9.8 11.7 0.84 (0.77, 0.92)
Region
Asia and Australia 1714 11.4 14.8 0.80 (0.61, 1.04)
Central and South America 1237 15.2 17.9 0.86 (0.65, 1.13)
Europe, Middle East and Africa 13859 8.8 11.0 0.80 (0.72, 0.90)
North America 1814 11.9 9.6 1.25 (0.93, 1.67)
ASA by median dose
>=300 956 15.8 10.7 1.45 (1.01, 2.09)
>100 - <300 1052 12.9 13.9 0.99 (0.70, 1.40)
<=100 15439 7.8 10.1 0.77 (0.69, 0.86)
Final Diagnosis
Unstable Angina 3112 8.6 9.1 0.96 (0.75, 1.22)
NSTEMI 7955 11.4 13.9 0.83 (0.73, 0.94)
STEMI 7026 8.5 10.1 0.84 (0.72, 0.98)
Planned Treatment Approach
Invasive 13408 8.9 10.6 0.84 (0.75, 0.94)
Medically 5216 12.0 14.3 0.85 (0.73, 1.00)
Actual Treatment Approach
Invasive treatment 11572 9.5 10.7 0.88 (0.78, 0.99)
Medical treatment 7052 10.4 13.3 0.79 (0.69, 0.91)
Early PCI (<24 hours after randomization)
No 9370 11.6 14.0 0.84 (0.74, 0.94)
Yes 9254 8.0 9.4 0.85 (0.74, 0.98)
Patients undergoing CABG after randomization
No 16725 9.2 10.9 0.84 (0.76, 0.93)
Yes 1899 15.4 18.0 0.89 (0.71, 1.12)
Diabetes History
No 13962 8.4 10.2 0.83 (0.74, 0.92)
Yes 4662 14.1 16.2 0.88 (0.76, 1.03)
Prior TIA/Stroke
No 17462 9.2 11.1 0.84 (0.76, 0.93)
Yes 1152 19.0 20.8 0.87 (0.66, 1.13)
Glycoprotein IIb/IIIa Inhibitor
No 13562 9.7 11.9 0.82 (0.74, 0.92)
Yes 5062 10.0 11.1 0.90 (0.76, 1.07)
Proton Pump Inhibitor Use at Randomization
No 12249 9.2 11.0 0.83 (0.74, 0.93)
Yes 6375 11.0 12.9 0.86 (0.75, 1.00)
Age Group
<65 years 10643 7.2 8.5 0.85 (0.74, 0.97)
>=65 years 7979 13.2 16.0 0.83 (0.74, 0.94)
<75 years 15744 8.6 10.4 0.82 (0.74, 0.91)
>=75 years 2878 16.8 18.3 0.94 (0.78, 1.12)
Sex
Male 13336 9.2 11.1 0.85 (0.76, 0.95)
Female 5288 11.2 13.2 0.83 (0.71, 0.97)
Race
Caucasian 17077 9.5 11.2 0.85 (0.77, 0.94)
Black 229 13.0 19.6 0.63 (0.32, 1.23)
Asian 1096 12.5 14.8 0.87 (0.62, 1.21)
Other 221 14.4 21.4 0.63 (0.33, 1.21)
0
0.5
1
1.5
2.0
Ticagrelor (Ti) Better
Clopidogrel (Cl) Better

So we do Subset analysis - Reasonably

1. We are not using them to discover whether the drug is effective or not. If overall results are negative, NEVER (almost, anyway) salvage with an unplanned subgroup analysis
2. We do not ask that effects in subsets be proved separately, e.g., by showing significance in M and F strata of each trial. But a pooled data overview of several trials often is large enough to detect differences that matter

3. Interest is in large, consistent difference in effect and, even then, subset differences are treated cautiously (there is some evidence that effects in men were smaller). Follow-up studies may be needed.

   Very unusual to use a subset analysis to exclude a group; aspirin was initially approved for stroke only in men, however, and it was an error). But see LIFE study below (losartan better than atenolol, except in blacks; ticagrelor should not be used with high-dose aspirin).

4. The statistical evaluation problems are formidable. A reasonable correction for multiplicity would eliminate almost all subset findings.

Demographic Subset Analyses

The subsets of greatest historical interest were demographic: age, sex, race. Stimulated first by interest in effects of age, we were urged in early 1980's to be sure older people were included in studies and analyzed . Thus in 1983 we proposed guidance on including the elderly (defined as 65 because written by a 42 year old). Became final in 1989 and then there was an ICH Elderly guidance (ICH E-7) in 1994, with a Q&A in 2010 emphasizing need to include people over 70.

In 1993 we produced a gender guidance (no similar ICH guidance) that, among other things, showed that women had not been excluded from clinical trials.

But the general idea of looking at demographic subsets had entered regulations [21 CFR 314.50] in 1985 as required analyses of the Integrated Summaries of Safety and Effectiveness.

History of Demographic Subset Analyses

314.50 (d)(5)(v) in 1985 called for "Integrated summary of the data demonstrating substantial evidence of effectiveness. . . The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different level of severity of the disease, also shall be presented."

314.50 (d)(5)(vi) "Integrated summary of all available information about the safety of the drug product. . . The safety data shall be presented by gender, age, and racial subgroups [and other subgroups when appropriate], such as for patients with renal failure or patients with different levels of severity of the disease."

Clin-Stat Guideline

1988 - Clin/Stat guideline (even before age and gender guidance) many references to subset analyses

Integrated Summary of Effectiveness

1. Overview: evidence pertinent to individualization of dosing and need for modification of dosing for specific subgroups; if relevant subgroups were not studied, this should be noted and implications considered.

2. Dose-response: "Any evidence of different D/R relationships in age, size, sex, disease, or other subpopulations, including evidence of different PK or PD responses." Describe how differences were looked for even if none were found.

Clin-Stat Guideline

3. Analysis of responses in subsets of the overall population: drug-demographic, drug-drug, and drug-disease interactions.

   The guidance notes these analyses have less weight than prespecified hypothesis, but urges looking anyway for consistent differences in effectiveness, dose, or PK among subsets, including sex, age, race, size, disease severity, concomitant illness, concomitant drug, smoking.

Later Documents

Clin Stat guideline (1988) was foundation of ICH E-3 [Structure and Content of Clinical Reports] (1996) and FDA Guidance on the Integrated Summary of Efficacy (ISE).

- E-3, focused on single studies, calls for presentation of demographic characteristics and, if the study size permits, examination of effects by age, sex, and race, as well as by prognostic features, severity, and other relevant features.
- ISE, guidance in 2008, specifically encouraged the use of pooled analyses to explore the effects of age, sex, and race, and other subgroup characteristics.
- FDA review template [MAPP 6010.3], 2004, calls for demographic analyses of the efficiency.
- FDASIA (2012) specifically urged more attention to these analyses.

So what do We Do?

In general, we study a broad population, drawing overall conclusions from that population, then examine the subgroups (age, gender, race, renal function, and “other”)

A model for presentation of subgroup data is the forest plot, which can look at many variables (recall ticagrelor), but, as noted, so far has been used only for outcome studies.

The easy part (PK)

I have just described the hard part of individualization,assessing PD or outcome differences in subgroups. The easy part is detecting PK differences (absorption, excretion, metabolism, drug-drug interactions), all of which are readily assessed.

Pharmacokinetic Screen

Proposed in 1983 "Discussion Paper," a proposal on how to evaluate drugs in the elderly. In the 1989 guideline it appears this way

> "Sponsors may . . . utilize a pharmacokinetic screen in conjunction with the phase 3 . . . clinical trials program. This screening procedure involves obtaining, under steady state conditions, a small number (one or two) of drug blood level determinations at "trough" . . . or other defined times from sufficient numbers of phase 2/3 clinical trials patients, geriatric and younger, to detect age-associated differences in PK behavior, if they are present."
>
> The advantage of the PK screen approach is that it can assess the effects, not only of age itself, but also of other factors associated with age (altered body composition, other drugs, concomitant illness) and their interactions.

This is, of course, population PK and, as noted, it is used with effectiveness data to model C/R relationships. It could be used (but usually has not) to assess subgroup differences in CR relationships.

PK Studies in Subsets

It is now routine to carry out specific PK studies in

- elderly
- M/F
- various degrees of renal failure
- various degrees of hepatic failure

Guidance on the last two

Blood Level Data

Of course, now we have blood levels on all patients (usually) and we understand and can evaluate almost all causes of PK differences

- Renal or hepatic function
- Metabolizing enzymes
- Drug-drug

A Few Examples

- Amlodipine
- LIFE Study
- Ticagrelor
- Fluoxetine effect on desipramine

Amlodipine

ADRs by Gender

	Amlodipine		Placebo	
	M(%)	F(%)	M(%)	F(%)
ADR	n=1218	n=512	n=914	n=336
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

Pooled placebo controlled trials, all doses

LIFE

Losartan vs. atenolol (n=9193) in hypertensives with LVH. Endpoint: time to CV death, non-fatal stroke, NFMI

Doses estimated as needed,

DBP>/ 90 mm Hg, or SBP>/ 140 mm Hg

Treatments	
Losartan 50	Atenolol 50
+12.5 mg HCTZ	+12.5 mg HCTZ
Losartan 100	Atenolol 100
+25 mg HCTZ	+25 mg HCTZ
+other (not BB, ACEI, AIIB)	+other (not BB, ACEI, AIIB)
BP 144.1/81.3	145.4/80.9

Results - LIFE

	Losartan N (%)	Atenolol N (%)	Risk Reduction	95% CI	P
Composite	508 (11)	588 (13)	13%	2-23	0.021
CV Mortality	125 (3)	134 (3)			
NF Stroke	209 (5)	286 (6)			
NF MI	174 (4)	168 (4)			
Individual Endpoint					
Stroke (F/NF)	232 (5)	309 (7)	25%	11 to 37	0.001
AMI (F/NF)	198 (4)	188 (4)	-7%	-13 to 12	0.491
CV Mortality	204 (4)	234 (5)	11%	-7 to 27	0.206
CHD	125 (3)	124 (3)	-3%	-32 to 20	0.839
Stroke	40 (0.9)	62 (1)	35%	4 to 67	0.032
Other	39 (0.8)	48 (1)	10%	-28 to 45	0.411

Results in Blacks			
	Losartan	Atenolol	HR (95% CI)
Composite	46/270 (17%)	29/263 (11%)	1.67 (1.004-2.56) p=0.03
Stroke	24/270 (9%)	12/263 (4.5%)	2.2 (1.079-4.401) p=0.03
Composite: black vs. non-black interaction p=0.005			

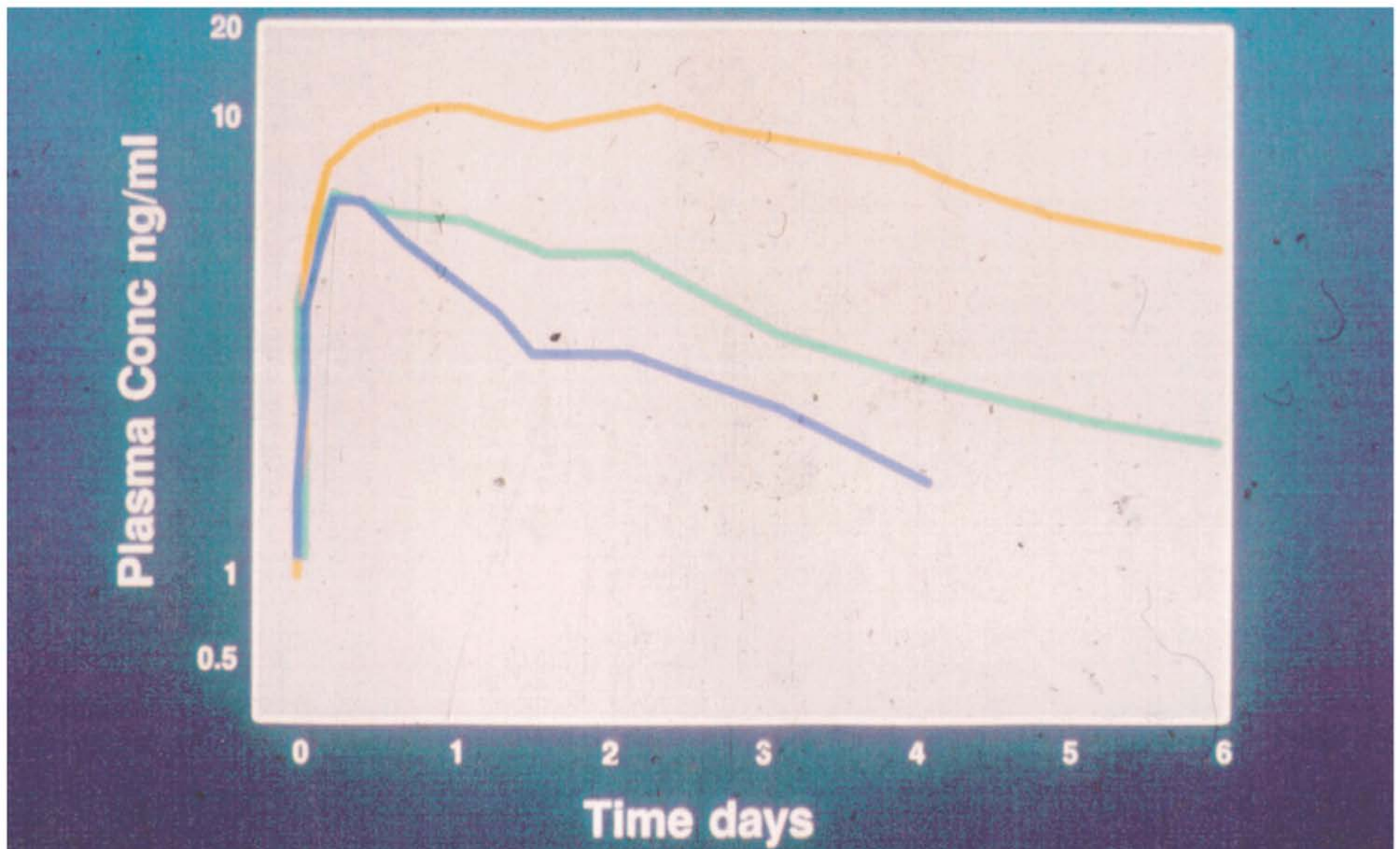


FIGURE 3. Mean plasma concentration values (n = 6) for desipramine (group 2) after a 50 mg imipramine dose given alone (□), after a single dose of fluoxetine (■), and after eight daily doses of fluoxetine (■).

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Thank You

Questions?

Comments?


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