Herbal/Drug Interactions

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11/12/09

Table 1. Enrollees in CHS Study[a]

Total enrolled: 5849
White: 4925 (84)
Black: 924 (16)
Male: 2478 (42)
Female: 3371 (58)

Study period	1	2	3	4
Total users	4373	4351	3919	3561
Rx users	3994 (91)	3891 (89)	3533 (90)	3259 (92)
CAM users	278 (6)	295 (7)	504 (13)	533 (15)
Vitamin/mineral users	1713 (39)	1707 (39)	1678 (43)	2081 (58)
OTC users	2635 (60)	2720 (63)	2263 (58)	2219 (62)
Rx plus CAM	238 (5)	243 (6)	411 (11)	463 (13)
Rx, CAM, OTC	264 (6)	270 (6.2)	459 (11.7)	511 (14.4)

[a] The number in parentheses is the percent of the enrolled

Elmer et al. Ann Pharmacother. 2007;40:1617-24.

Table 4a Significant Risk of CAM-drug Adverse Interaction n=5052 (16,173 interviews)

Potential Event		Mechanism[a]	Number[b]	Occurrences[c]
Risk of bleeds				
Aspirin			no. patients	all occurrences
	Garlic[23;25-27]	PD	147	214
	Ginkgo[24;28]	PD	102	127
Warfarin				
	Garlic[25-27]	PD	13	16
	Ginkgo[29]	PD	7	7
	Ginseng[32;33]	PK[d]	3	3
Ticlopidine				
	Garlic[23;25-27]	PD	4	6
	Ginkgo[24;30;31;54]	PD	2	3
Pentoxifylline				
	Ginkgo[24;30;31]	PD	3	3
Total		281 (5.6%)	380	

Elmer et al. Ann Pharmacother 2007;41:1617-1624

Table 4b
Significant Risk of CAM-drug Adverse Interaction

Potential Event	Mechanism[a]	Number[b]	Occurrences[c]
Decreased drug benefit			
Digoxin			
St. John's wort[21;34]	PK[e]	2	2
Felodipine			
St. John's wort[21;52]	PK[f]	2	2
Tamoxifen			
Garlic[41]	PK[f]	4	5
Other			
Furosemide/Aloe[55]	PD	3	3
Thyroid/Kelp[56]	PD	2	2
Grand Total		294	393
Garlic interactions:		168	241
Ginkgo interactions:		114	140
Garlic plus ginkgo:		282 (96%)	381 (97%)

Elmer et al. Ann Pharmacother 2007;41:1617-1624

Steps for Detecting and Advising on Herbal/Drug Interactions

- Is the patient taking any herbal supplements?
- Does the herbal have efficacy for the intended use?
- Is the product reliable? (i.e.,what are they REALLY taking?)
- Is the Rx drug one with a narrow therapeutic margin?

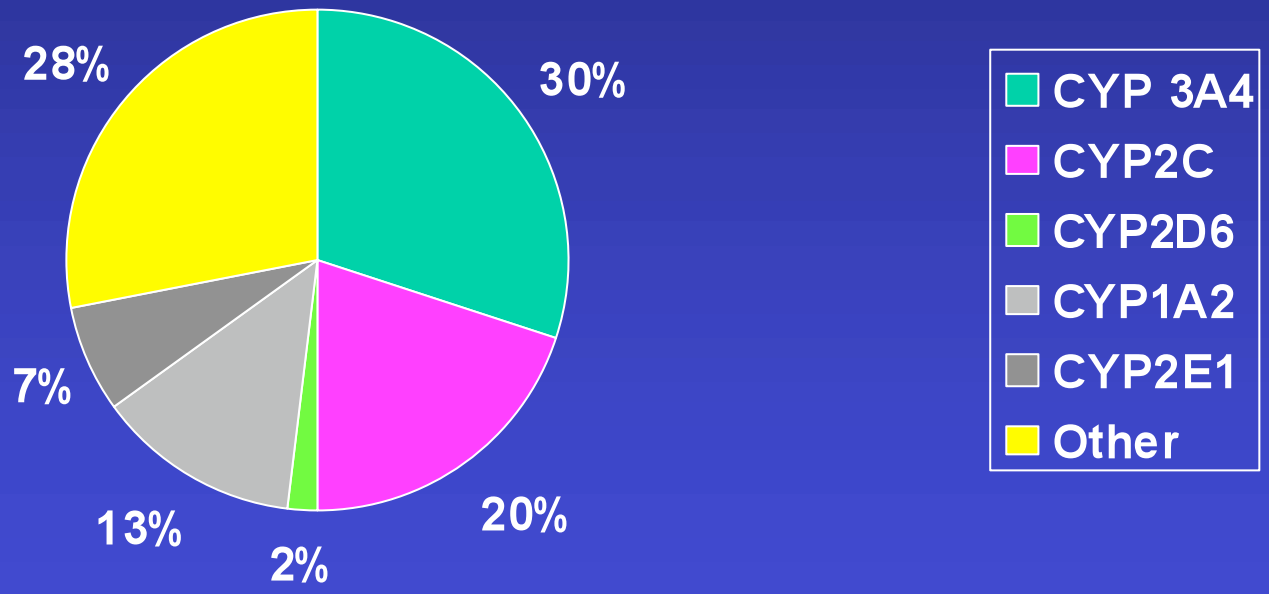
Evaluation of Herbal/Drug Interactions

- Speculative or Theoretical
  - e.g. St. John's Wort and tyramine containing foods due to MAOI effects or evening primrose oil and risk for bleeds with warfarin
- In vitro effects
  - e.g. ginkgo and microsomal studies showing inhibition of CYP2C9
- In vivo - animal studies
  - e.g. kava and alcohol
- In vivo - human case reports
  - e.g. ginkgo and warfarin bleeds
- In vivo - healthy human volunteer studies
  - e.g. indinivir and St. John's Wort
- In vivo - clinical studies in patients

Important Criteria for Evaluation of a Human Herbal/ Drug Interaction Report

- Reputable standardized product used and carefully described?
- Product used analyzed for marker compounds?
- Same batch used throughout study?
- Doses appropriate?
- Steady state study to discern CYP induction?
- Is observation consistent with known mechanisms of action?
- Is observation consistent with literature observations?
- Randomized, placebo controlled human volunteer study with appropriate n?

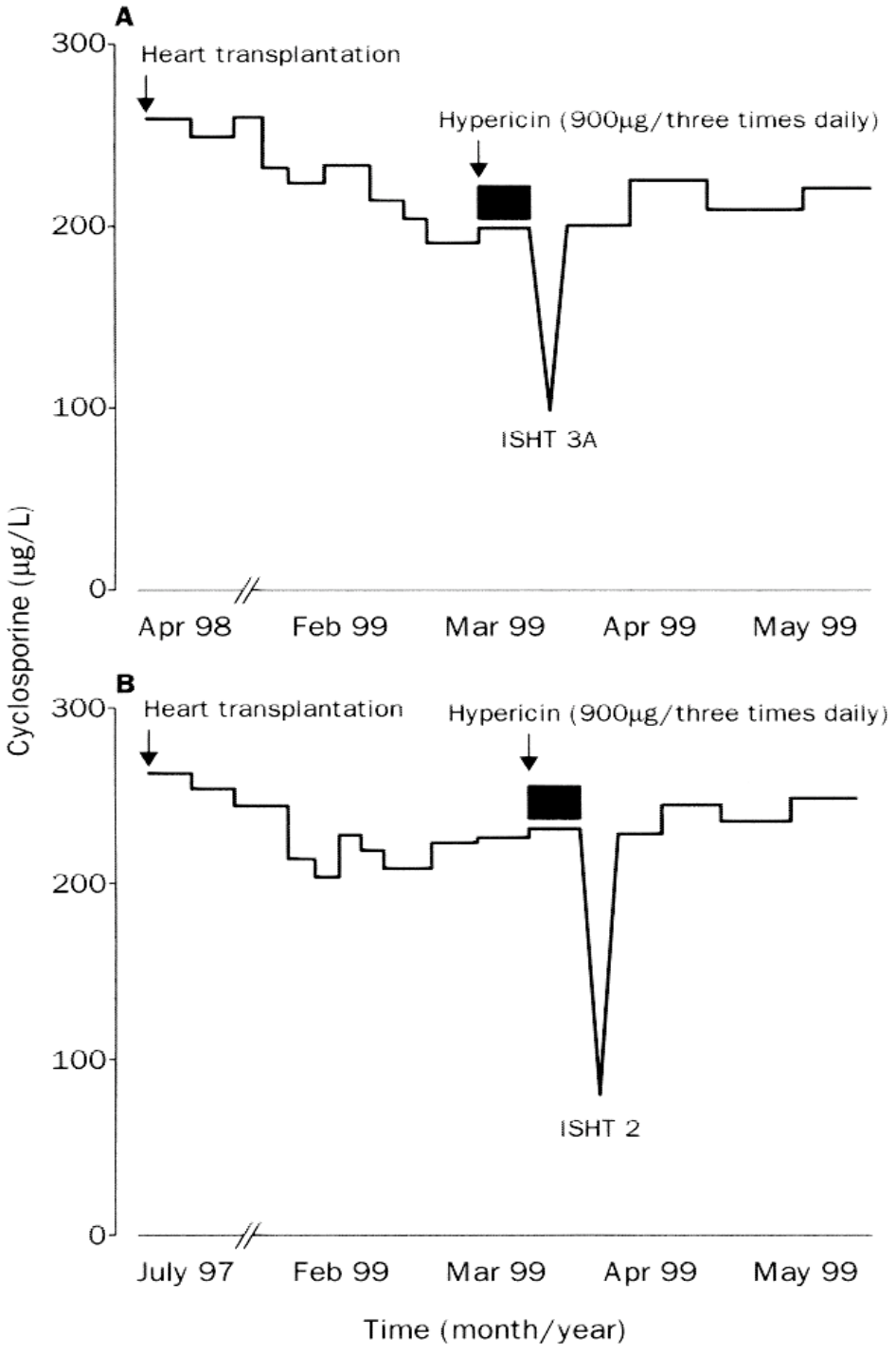
Relative Levels of P450 isozymes in human liver



Interactions with St. John's Wort -cyclosporin-

- Study: 2 case reports
  - case 1: 61yr had transplant 11mos earlier; cyclosporin, azathioprine, steroids for 11 mos. Unexplained heart failure noted after SJW started.
  - case 2: 63yr had transplant 20mos earlier: same senario as case 1.

Ref: Ruschitzka et al. Lancet 355:548-549,2000


A
300
200
100
0
Heart transplantation
Hypericin (900µg/three times daily)
ISHT 3A
Apr 98
Feb 99
Mar 99
Apr 99
May 99
B
300
200
100
0
Heart transplantation
Hypericin (900µg/three times daily)
ISHT 2
July 97
Feb 99
Mar 99
Apr 99
May 99
Cyclosporine (µg/L)
Time (month/year)

Summary of SJW Interactions

(adapted from Henderson et al. Br J Clin Pharmacol 2002;54:349-346)

Drug	CYP	Effect	Management
HIV protease inhibitors (nelfinavir,ritonavor,saquinavir)	Induce 3A4	↓	Stop and measure viral load
HIV non-nucleoside RTI (efavirenz,nevirapine)	Induce 3A4	↓	Stop and measure viral load
warfarin	Induce 2C9	↓	Stop and adjust warfarin dose
cyclosporin	Induce P-glycoprotein	↓	Stop and adjust cyclosporine dose
oral contraceptives	Induce 3A4	↓	Stop and use alternate birth control
anticonvulsants	Induce 3A4	↓	Stop and adjust anticonvulsant dose
digoxin	Induce P-glycoprotein	↓	Stop and adjust digoxin dose
theophylline	Induce 1A2	↓	Stop and adjust theophylline dose
Triptans (sumatriptan)	Increase serotonin	↑	Stop
SSRI (fluoxetine,sertraline, etc)	Increase serotonin	↑	Stop

St. John's Wort

- Summary
  - Efficacy: good evidence for mild to moderate depression
  - Safety: don't combine with other medications unless under close monitoring; possible photosensitivity
  - Drug interactions: a problem! Is a broad spectrum P450 inducer and a p-glycoprotein inducer.
  - Product selection: want standardized extract containing about 0.3% hypericin or 1-2% hyperforin
  - Dose: about 300mg TID for treatment
  - GWE: avoid concurrent use with all but the safest of drugs

Bleeds associated with ginkgo use

Patient age	Ginkgo use	Other therapy	Bleed	ref
70	1 week	Aspirin	Iris	1
78	2 mos	Warfarin	Intracerebral	2
33	2 years	None	Subdural	3
61	6 mos	None	Subarachnoid	4

1. NEJM 336:1108,1997
2. Neurology 50:1933-1934,1998
3. Lancet 352:36-37,1998
4. Neurology 46:1775-1776,1996

Ginkgo-warfarin interactions?

Non-linear Regression

K_i Values

Isoform	Type of Inhibition	Ki (μg/ml)	α
CYP1A2	Mixed	11.2	0.6
	Competitive	2.1	---
CYP2A6	Mixed	21.2	2.1
CYP2C9	Competitive	9.1	---
CYP2D6	Competitive	133.1	---
CYP3A4	Mixed	17.0	2.5

Mohutsky et al. Am J Ther 2006;13:24-31

Tolbutamide Human Study (CYP 2C9 probe)

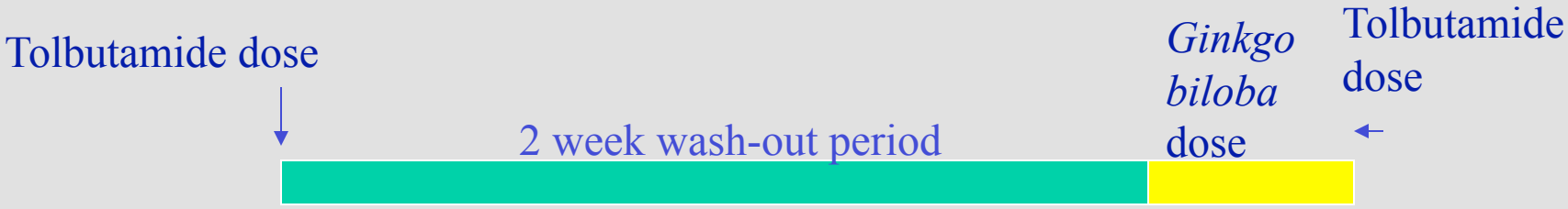
- **6 Subjects (3 males, 3 females)**

-Subjects ingested 500mg tolbutamide and collected 6-12 hour urine (Control phase)

-Followed by a 2 week wash-out period

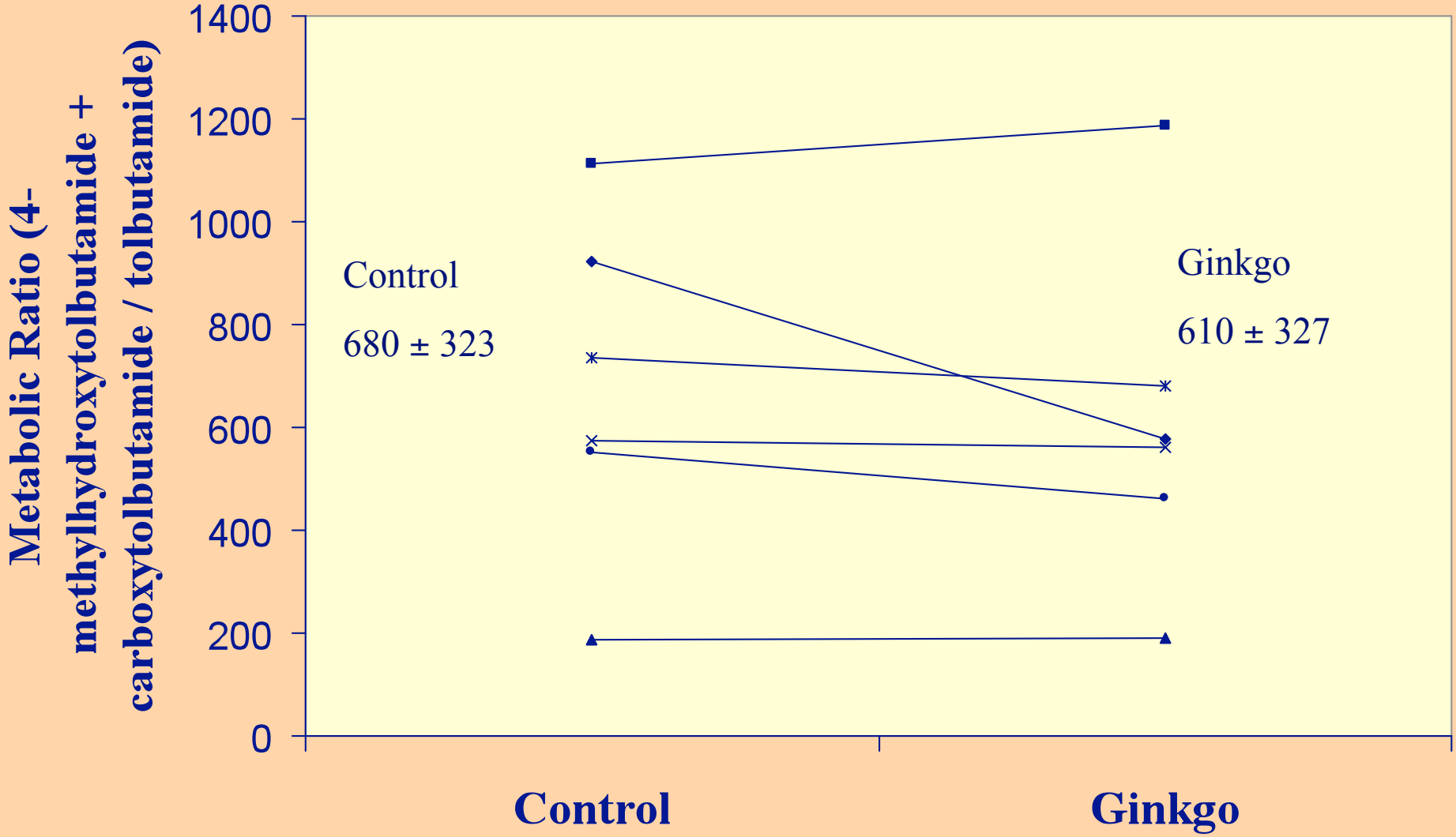
-Subjects then ingested two 60mg *Ginkgo biloba* extract tablets 2 times a day for 3 days

-The morning of day 4 patients received a 500mg dose of tolbutamide along with the ginkgo and collected 6-12 hour total urine (Ginkgo phase)



Mohutsky et al. Am J Ther 2006;13:24-31

Comparison of Tolbutamide Metabolic Ratios



Mohutsky et al. Am J Ther 2006;13:24-31

Diclofenac-Ginkgo Interaction (CYP 2C9 probe)

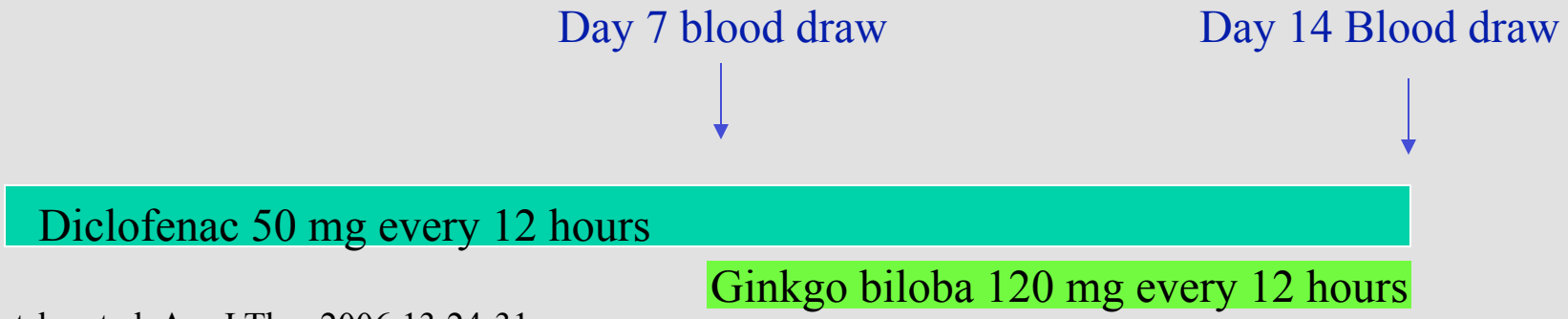
12 healthy non-smoking subjects were recruited (8 males 4 females)

50 mg diclofenac potassium (immediate release) was administered every 12 hours for 14 days

On day 8, 120 mg of *Ginkgo biloba* extract was added to the diclofenac regimen.

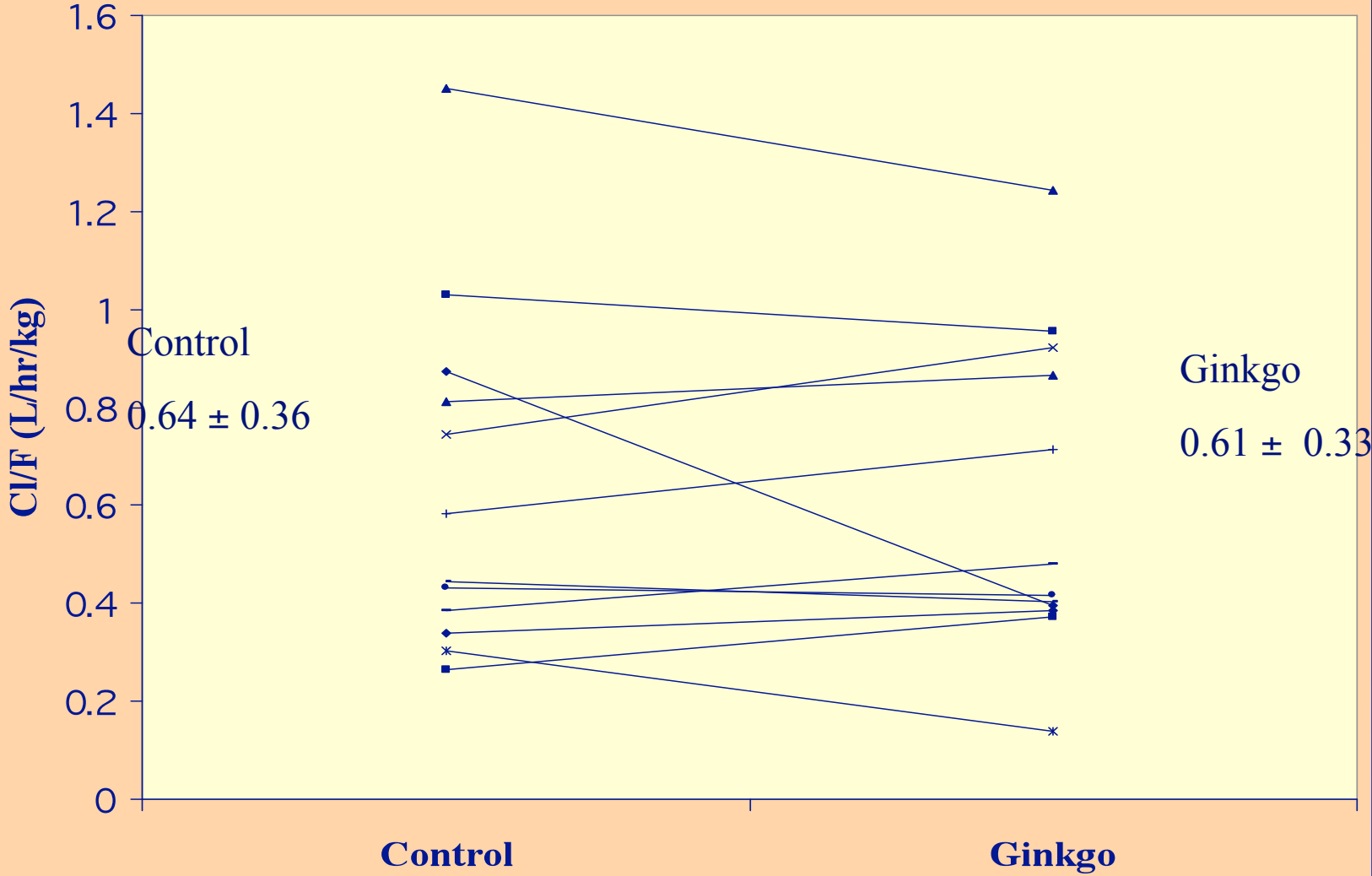
On days 7 and 14 plasma collected at times (0, 0.5, 1,2,4,6,8,10, and 12 hrs)

12 hour urine collected



Mohutsky et al. Am J Ther 2006;13:24-31

Comparison of Diclofenac Clearances from Plasma



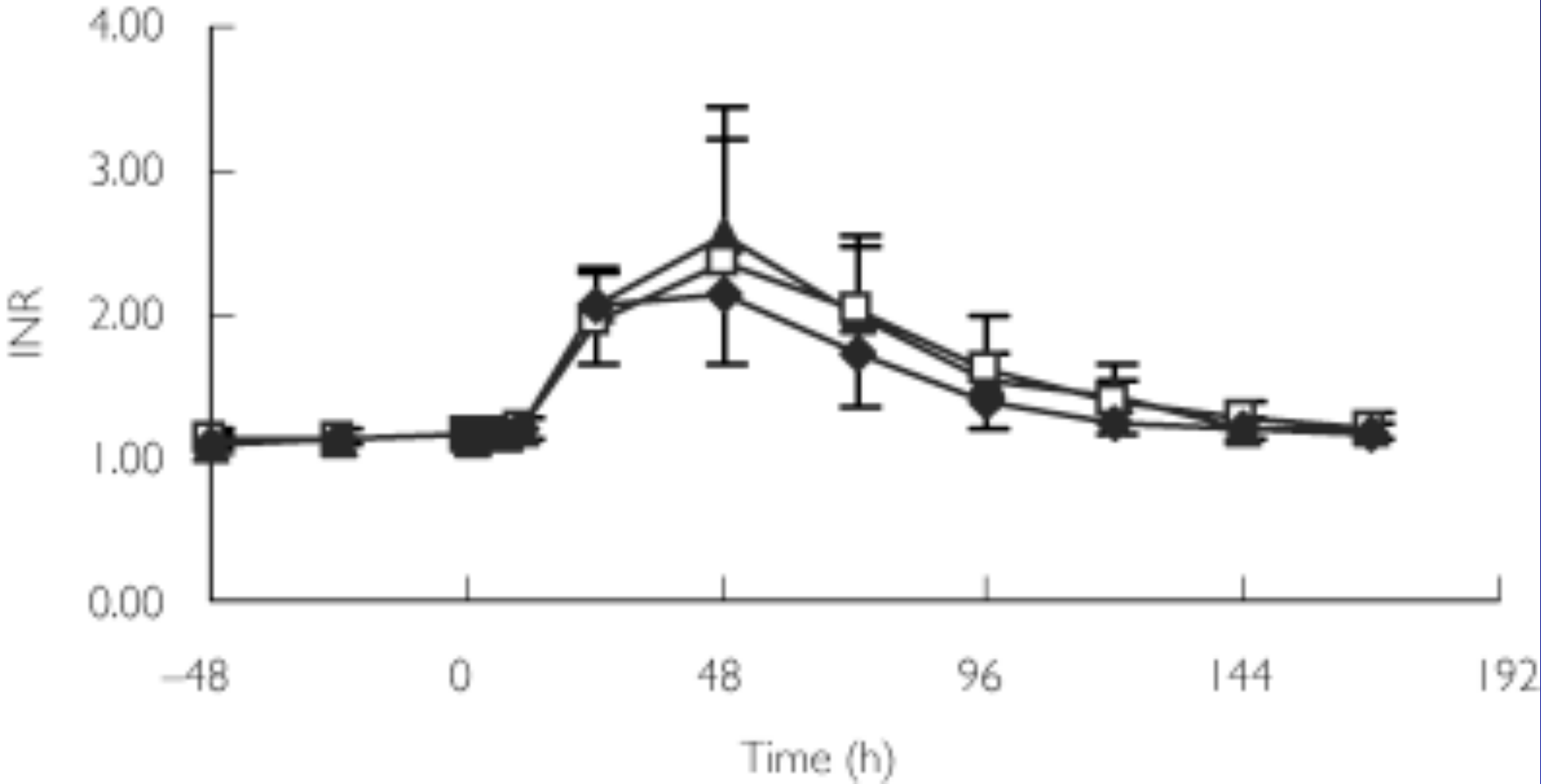
Mohutsky et al. Am J Ther 2006;13:24-31

Ginkgo biloba - Diclofenac Tolbutamide Human Studies Conclusions

- No difference was observed in the metabolic ratio between the two arms of the study (tolbutamide alone and tolbutamide + Ginkgo)

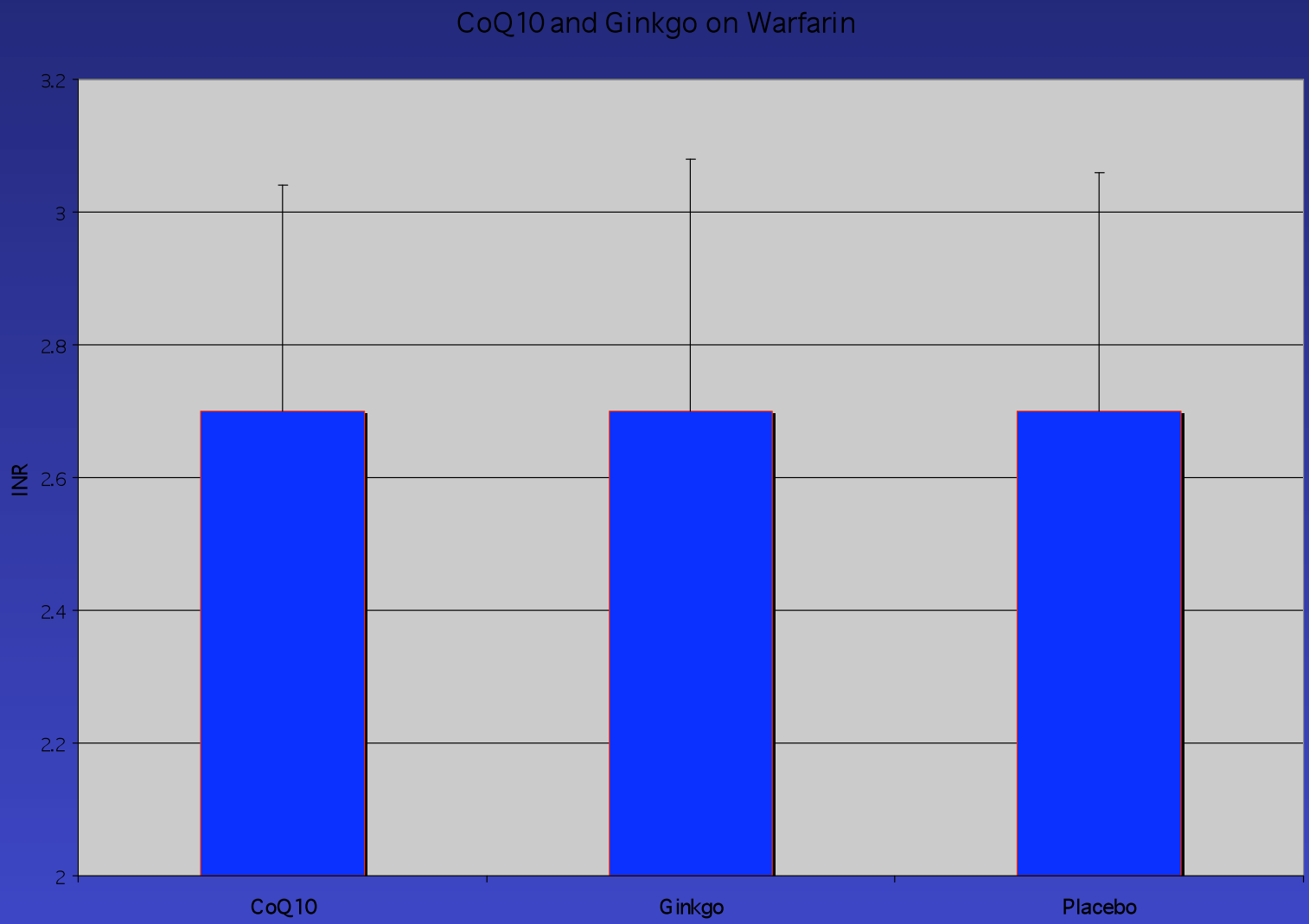
- No difference was seen between the clearances of the two arms of the study (diclofenac alone and diclofenac + Ginkgo)

- Ginkgo extract does not appear to interact with CYP2C9 substrates in humans



Jiang et al. Br J Clin Pharmacol 2005;59:425-432.

N=12 ginkgo for 7d; warfarin alone or in combination with ginkgo or ginger



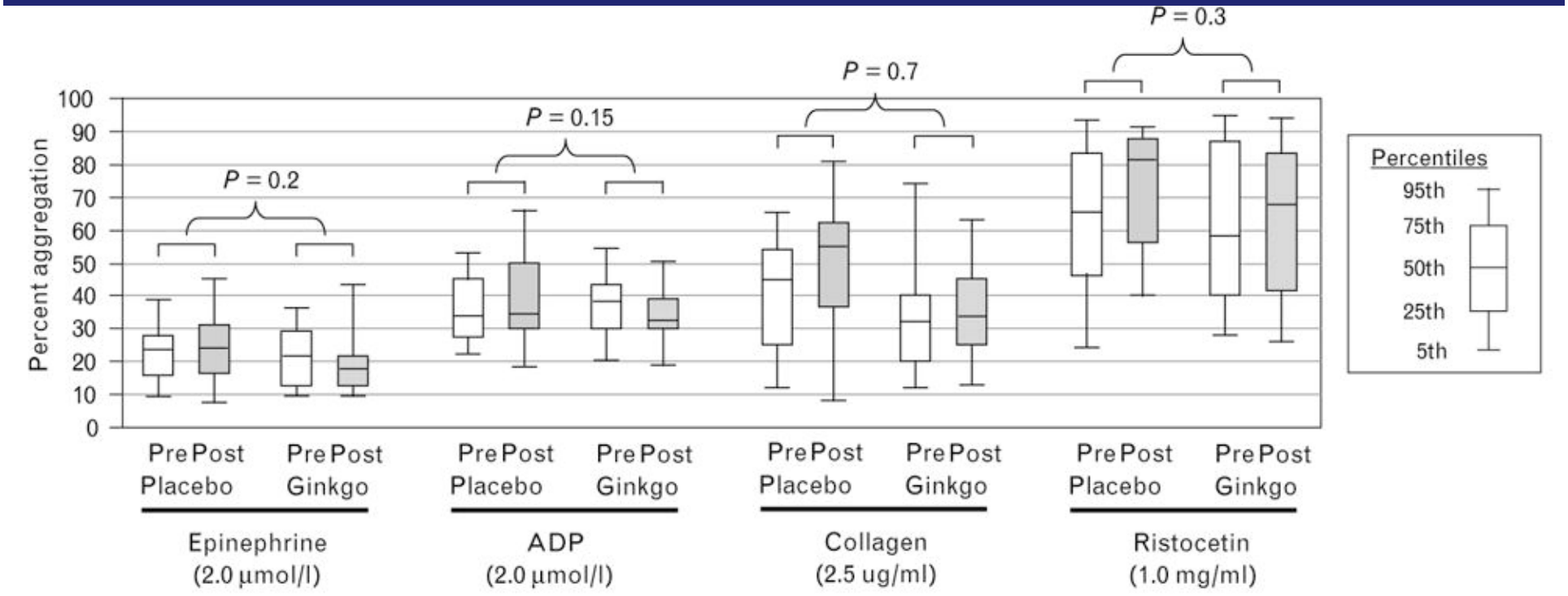
Engelsen et al, Thromb Haemost 2002;87:1075-6. N=21, double blind, crossover. Rx=1 month with 2 week washout. Dose of warfarin did not change.

Ginkgo and coagulation and pharmacodynamic interactions with antiplatelet adhesion inhibitors

Coagulation in healthy adults (in absence of other drugs)

Kohler et al. Blood Coagul Fibrinolysis. 2004;15:303-9. (company study).

No effect on coagulation parameters in healthy adults after 7d of EGb761 120mg/d. n=50.



Platelet aggregation. Box-and-whiskers plots of percentage platelet aggregation for placebo ($n = 21$) and ginkgo ($n = 23$) groups for prestudy (white shading) and end-study (gray shading), using four agonists. Analysis of variance with two treatments and two time points. *P* values presented are for the treatment × time interaction. Statistical significance was not found with any of the four agonists.

Gardner et al. Blood Coagul Fibrinolysis 2007;18:287-293

Aspirin 325mg/d for two weeks prior to 4 weeks Ginkgold 300mg/d

Close this Window

Aruna, D. & Naidu, M. U. R.
Pharmacodynamic interaction studies of *Ginkgo biloba* with cilostazol and clopidogrel in healthy human subjects.
British Journal of Clinical Pharmacology **63** (3), 333-338.
doi: 10.1111/j.1365-2125.2006.02759.x

Table 3

Bleeding time (s)

	Mean	SD	SE	95% CI (lower)	95% CI (upper)
Baseline, *n* = 80	107	33	4	99	115
Cilostazol 100 mg (*n* = 10)	150*	42	14	118	182
Cilostazol 200 mg (*n* = 10)	138**	30	10	115	161
Ginkgo 120 mg (*n* = 10)	144*	28	9	124	164
Ginkgo 240 mg (*n* = 10)	133*	30	10	110	157
Clopidogrel 75 mg (*n* = 10)	141	59	21	91	190
Clopidogrel 150 mg (*n* = 10)	159*	56	20	113	206
Clopidogrel + Ginkgo (*n* = 10)	148*	78	28	83	213
Cilostazol + Ginkgo (*n* = 10)	211*†	70	25	153	270

**P < 0.05 compared with baseline. **P < 0.001 compared with baseline. †P < 0.05 compared with 150 mg of clopidogrel.*

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Bleed times; single dose n=80 cilostazol=Pletel clopidrogrel= Plavix

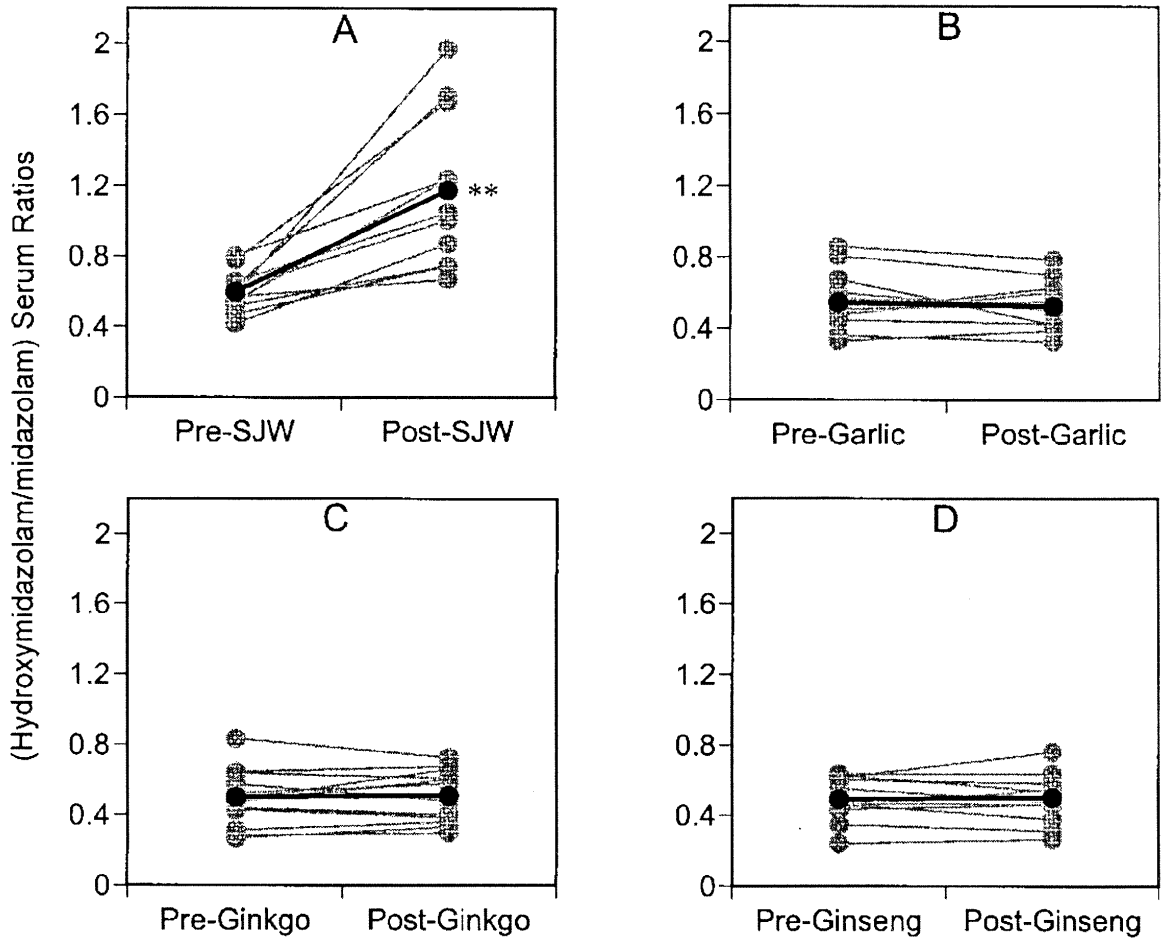
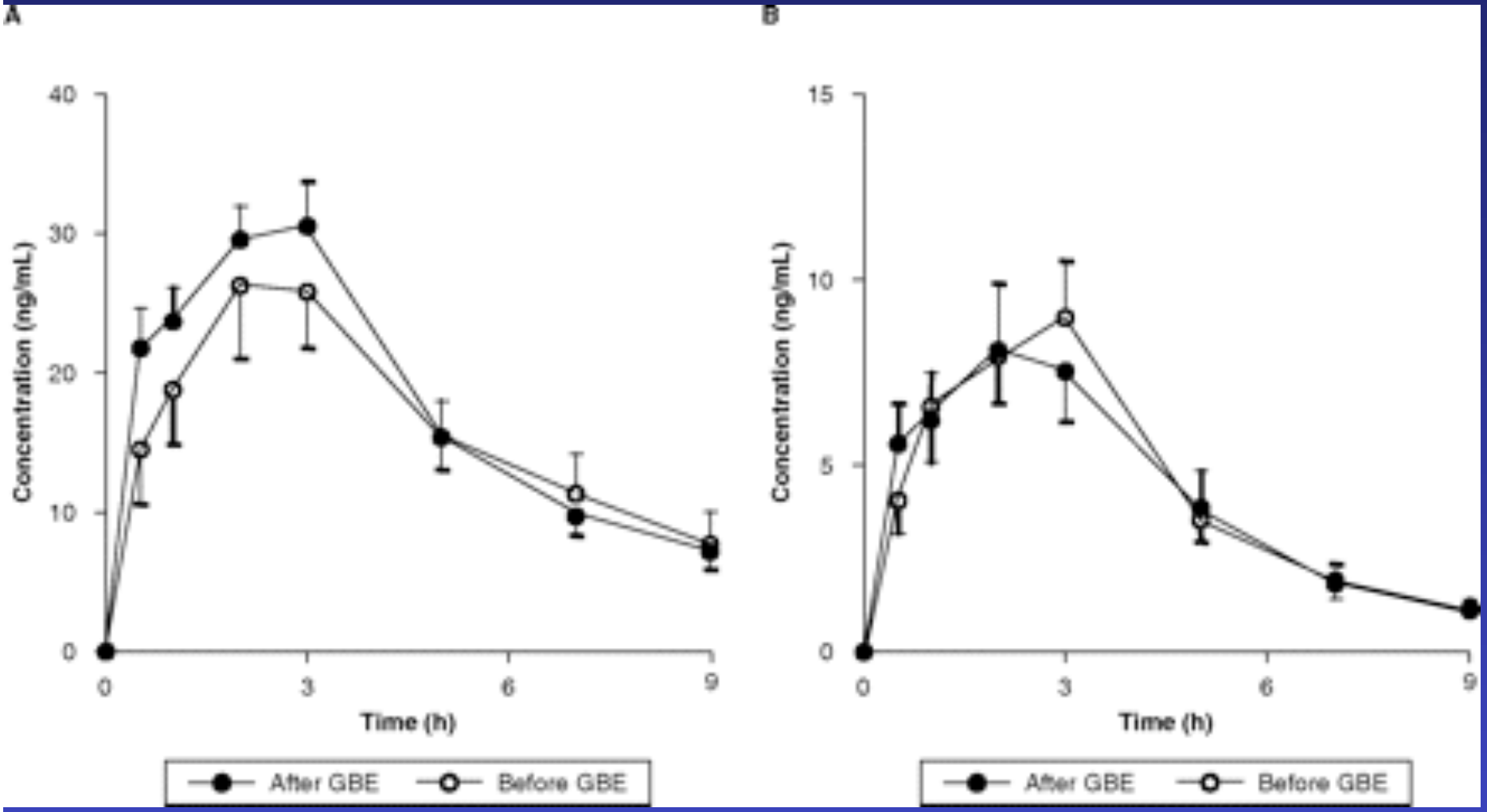


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically significant difference from baseline.

Gurley et al. Clin Pharmacol Ther 2002;72:276-287 n=12 (CYP 3A4)
ginkgo-Wild Oats Markets (24% flavone glycosides, 6% ginkgolides)
(analyzed)



Ushida et al. J Clin Pharmcol 2006;46:1290-8 n=12 CYP 3A4 probe is midazolam; note: use Ginkgold 120mg TID!

Ginkgo biloba summary

- **Efficacy**: questionable for dementia and peripheral circulatory problems
- **Safety**: good; rare bleeding episodes
- **Drug interactions**: no effect on 3A4,2C9 or 2D6 but may induce 2C19 omeprazole study); inhibits platelet adhesion; *possible* (not necessarily probable!) interaction with platelet drugs and warfarin so avoid or close monitoring needed.
- **Product selection**: look for EGb761 extract
- **Dose**: 1-2 60mg tabs, BID
- ***GWE:*** to be on the safe side, best to avoid use with warfarin, aspirin, and platelet drugs.

Garlic summary

- **Efficacy**: ? benefit for use in hyperlipidemia. Possible other cardiovascular benefits.
- **Safety**: good
- **Drug interactions**: warfarin; possibly aspirin and other antiplatelet adhesion drugs (pharmacodynamic interaction); not with HIV drugs (other 3A4 substrates?) but depends on product (pharmacokinetic interaction) (maybe raw garlic induces 3A4 but not extracts??)
- **Product selection**: Suggest enteric coated tablets standardized to about 4mg allicin yield/ tablet
- **Dose**: equivalent of about 4g (2-3 cloves) of fresh garlic per day i.e. 8-12 mg allicin/d
- ***GWE**: garlic supplements should be avoided with warfarin (and possibly antiplatelet drugs) and HIV drugs*

Soy

- **Efficacy: increased soy ingestion may decrease hot flashes and other postmenopausal symptoms; cardiovascular benefits as well.**
- **Safety: good but use in breast cancer may be risky**
- **Drug interactions: not with with tamoxifen but effect on CYP3A4 is unlikely**
- **Product selection: soy or isoflavones**
- **Dose: about 20-40g of soy protein has been used. This contains 30-50mg of isoflavones.**
- **GWE:** not with tamoxifen but otherwise OK

Ginseng

Efficacy: some evidence for applications in geriatric patients (improved "quality of life") and in diabetes

Safety: good;

Drug interactions: no apparent induction of CYP 3A4 but induction of 2C9 (warfarin) with Am ginseng (Panax quinquifolius) but maybe not Panax ginseng. May precipitate hypoglycemia with insulin or oral hypoglycermics.

Product selection: product should be standardized so dose is 4-7% ginsenosides/d

GWE: safest to avoid use with warfarin and hypoglycemics

Echinacea

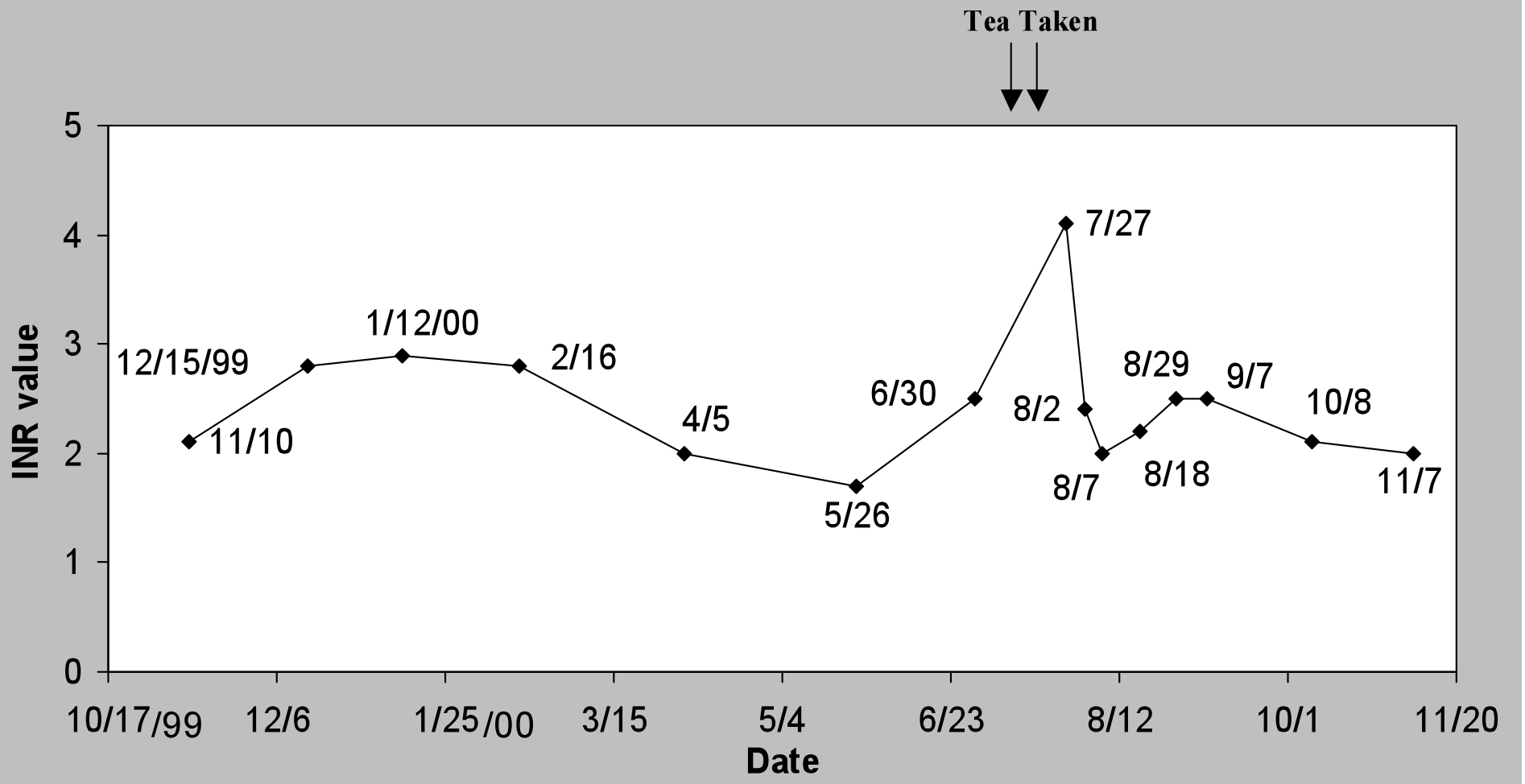
- **Summary**
  - **Efficacy: evidence for treatment not prevention**
  - **Safety: good; rare allergy**
  - **Drug interactions: Pharmacodynamic: don't give to patients taking immunosuppressive drugs**
  - **Pharmacokinetic: may inhibit 1A2; may inhibit intestinal 3A4 but induce hepatic so clinical significance unclear; effect on 2C9 is considered minor**
  - **Product selection: want standardized extract containing about 4% phenolics. *(GWE recommends Echinamide in 2008)***
  - **Dose: about 250mg QID for treatment**
  - ***GWE: echinacea/drug interactions are only of minor concern***

Herbs with clotting problems reported in humans

Ginkgo and garlic and St. John's wort- see earlier notes

Evening primrose oil -	human study showed 40% increase in bleed time but no other reports
Borage seed oil -	same as evening primrose oil
Vitamin E -	doses >1200 i.u./d can increase bleed time
Cranberry juice	case reports of increased INR (salicylic acid? CYP 2C9 inhibition?) but in vivo study showed no change in flurbiprofen (CYP 2C9 substrate) in vivo
Lycium barbarum	case report of increased INR
Danshen -	case reports of increased INR with warfarin
Dong quai -	case reports of increased INR with warfarin
American Ginseng -	decreased INR with warfarin (Panax quinquifolius)
Green tea -	case report of decreased INR with warfarin but huge amount
CoQ10 -	case reports of decreased INR with warfarin but human study showed no effect on INR
Glucosamine-	increased INR cases with warfarin
Chondroitin-	increased INR cases with warfarin

Fig. 1 Patient INR Values



From: Lam AY, Mohutsky MA and Elmer GW. Probable herbal/drug interaction between warfarin and a common Chinese herb, Lycium barbarum. Ann Pharmacother 2001;35:1199-1201

Gary Elmer's assessment of herbal/drug interaction potential (in rank order of significance)(11/13/09)

1. St. John's wort – induces CYP and Pgp; don't take with other drugs unless the drugs have a large therapeutic range and are not "life saving" drugs

2. American ginseng (Panax quinquefolius) – induces CYP2C9; not with warfarin, tolbutamide and other 2C9 substrates;

3. Goldenseal – induces CYP3A4 and 2D6. This herbal is not recommended due to lack of efficacy proof and potential interactions

4. Garlic and ginkgo – don't take with antiplatelet adhesion drugs or aspirin or with warfarin (risk of bleeds); this is a pharmacodynamic effect. Risk may be over stated based on recent evidence.

5. Ginkgo may induce CYP2C19 so may lower 2C19 substrates like omeprazole, phenytoin and diazepam

6. Echinacea may induce CYP1A2 so may lower 1A2 substrates like caffeine, theophylline and acetaminophen

Seem to have low pharmacokinetic drug interaction potential based on recent studies

- Ginger
- Valerian
- Milk thistle
- Saw palmetto
- Black cohosh
- CoQ10

References with Good Herbal/Drug Interactions Discussion

- **"Top 100 Drug Interactions"** Hansten PD and Horn JD. H&H Publications 2008

- **Natural Medicines Comprehensive Database.**
  Online version updated "daily". UW Healthlinks http://www.naturaldatabase.com/; $92

Recent Reviews

- Izzo AA and Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777-98
- Skalli S, Zaid A, Soulaymani R. Drug interactions with herbal medicines. Ther Drug Monit. 2007 Dec;29(6): 679-86
- Chavez ML, Jordan MA, Chavez PI. Evidence-based drug--herbal interactions.Life Sci. 2006;78:2146-57.

What can we do?

- **dialog with NDs and other prescribers**
- **recommend the best products**
- **ask patients about herbals they may be taking**
- **herbals should not usually be recommended for acute or serious illnesses**
- **avoid herbal use with drugs with narrow therapeutic window,** esp. warfarin, cyclosporin, digoxin, HIV protease inhibitors, theophylline, carbamazepine
- **stay informed**