Problems with a belly? Just give it a PAT

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student
6 Feb 2014

Case

- 26 yo male
- PMHx: developmental delay, seizure disorder
- Current medications:
  - Valproic Acid 1500mg PO BID
  - Phenytoin 400mg PO qHS
  - Clobazam 15mg PO BID
    - Started 3 months prior during admission for intractable seizure
    - After addition, daily seizures decreased from 5-6 to 1-2

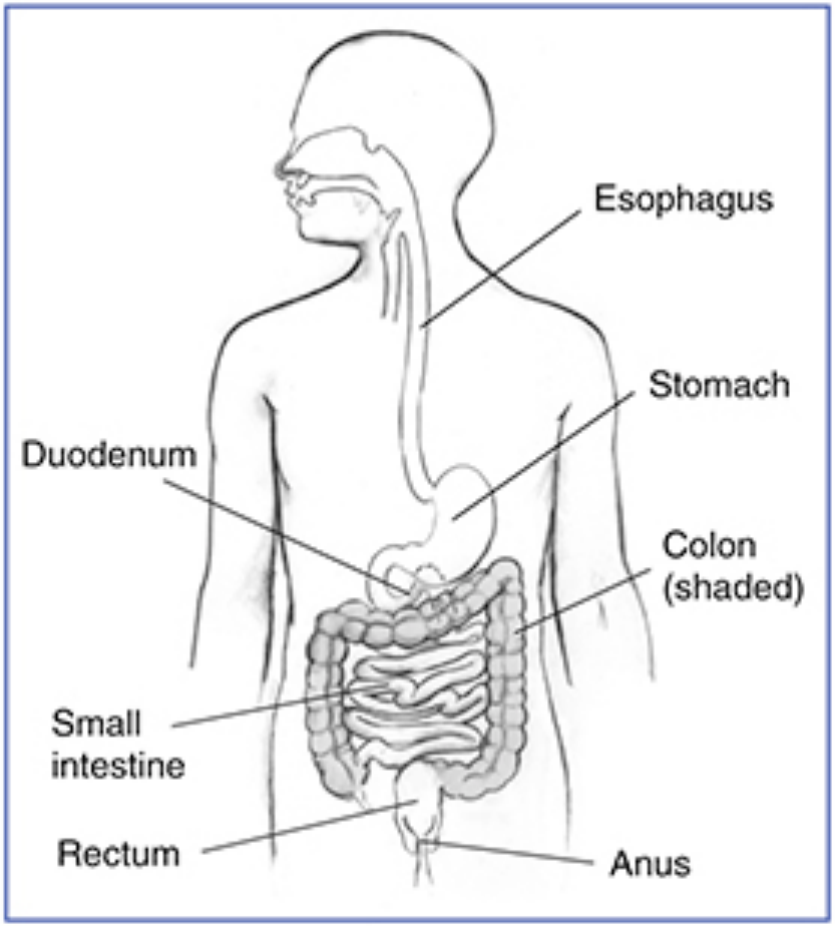
Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Case (cont)

- CC: Urosepsis → Septic shock
  - ICU admission, vasopressors, mechanical ventilation
- AM rounds:
  - RASS -1
  - No seizure activity overnight
  - No bowel sounds
  - Feeds via NG at 70 mL/h
  - Gastric Residual 220 mL
  - Abdomen distended
- Is he at risk of not being able to absorb anti-seizure medications?

The GI tract

- Chief route of absorption:
  - Nutrition
  - Drugs
- Absorption affected by:
  - Decreased blood flow
    - Vasopressors
  - Altered gastric motility
    - Opioids
  - Feeding tube and feed interactions



http://trialx.com

Jonathan Mailman, BSc(Pharm), ACPR,
PharmD Student

Ukleja, A. Nutr in Clin Pract 2010;25(1):16-25
Brian S. Smith CHEST 2012; 141(5):1327–1336

Altered motility in ICU

- Up to 60% experience dysmotility in ICU
  - Decreases nutrition delivery
  - May alter drug delivery
- Patients not tolerating feeds at risk:
  - Aspiration (micro vs macro)
  - Increased length of ICU stay
  - Increased mortality

- If intolerant to feeds, able to absorb drug?

Jonathan Mailman, BSc(Pharm), ACPR,
PharmD Student

Chan et al. Nutr in Clin Pract 2010;25(1):10-12
Landzinski et al. JPEN 2007;32(1): 45-50

Need to Give Therapy and Unsure if Gut is Absorbing

- No IV access
- Peripheral IV only and drug causes thrombophlebitis
- Parenteral formula is not available/ideal
  - eg clobazam

- How to assess gastrointestinal function?

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PharmD Student

Is the Gut Functioning?

- If giving a medication that normally is therapeutically monitored … TDM!

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PharmD Student

Bowel Sounds

- Peristalsis may occur without bowel sounds
  - May occur silently post-ileus
- Sounds not associated with tolerating feeds
  - Air movement in the GI tract
- During ileus, bowel sounds:
  - absent
  - Hypoactive
  - high-pitched

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Shibata. World J. Surg. 1997;21:806–810
Heyland. Clin Int Care 1996;7:68-73
Ukleja. Nutr Clin Pract 2010;25:16-25

Gastric Residual Volume

- Affected by:
  - Technique
  - Patient position
  - Tube location
  - Tube diameter
  - Number of syringes used

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

McClave et al. Crit Care Med 2005;33:324 –330
Horn et al. Aust Crit Care 2004;17(3):98-100, 102-3
Burd and Lentz. *Nutr Clin Pract* 2001;16:349-354
Mentec et al. Crit Care Med 2001; 29:1955–1961

Gastric Residual Volume

- Lack of standard "max volume" cut off
  - Patients with low residuals still aspirate
  - Patients with high residuals tolerate feeds
- Why do we like it?
  - Easy to obtain
  - Is a number
- Ignore it?

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Landzinski et al. JPEN 2008;32(1):45-50
MacLaren et al. JPEN 2008;32(4);412-419
Jooste et al. Int Care Med. 1999;25:464-468
Heyland et al. AM J Respir Crit Care Med 1996;154:1678-1683

Scintigraphy

- Scintigraphy (*gold standard)
  - Radio-labelled meal (Indium or Technetium)
  - Observed with gamma-camera for 2-4 hours
- Detecting delayed gastric emptying at 4 hours:
  - 100% sensitivity
  - 70% specificity
- Pro: Non-invasive, observe anatomical and physiological aspects of GI tract
- Con: Cost, availability of equipment, time required (2-4h), radiation dose with repeat testing, requires nuclear medicine involvement

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Moreiri et al. *Nutr Clin Pract* 2009;24:261-273
Thomforde et al. *J Nucl Med* 1995;36(1):93-6.

Assessing GI Function

- Carbon-13 Breath Test
  - Pro: Non-invasive
  - Con: Indirect measurement of GI function, availability of equipment, labour intensive
- Ultrasound
  - Pro: Non-invasive, equipment widely available
  - Con: Fasted baseline required, technique, lack standardization, difficult with large body habitus
- Gastric Impedance Monitoring
  - Pro: Non-invasive, easy administration
  - Con: Fasted baseline required, special standardized meal required, equipment availability

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Moreiri et al. *Nutr Clin Pract* 2009;24:261-273

Just Give Them a PAT

- Acetaminophen primarily absorbed in small bowel
- Acetaminophen given, serial serum levels, AUC calculated
  - $AUC_{60} \geq 600$ mg.min/L considered normal gastric emptying
- Serum levels may indicated delayed gastric emptying
  - Longer Tmax, lower Cmax, smaller AUC
- Con:
  - Must assume acetaminophen is a sufficient analogue
    - Absorption
    - Physiochemical properties
  - Potentially giving unnecessary drug

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Heading et al. Br J Pharmac. 1973;47:415-421
Cohen et al. Clin Nutr. 2000;19:233–236
Berger et al. J Par Ent Nutr 2003;27:151–155

Clinical Question

- In a patient with a potential gastrointestinal dysmotility, how does the paracetamol absorption test compare to the gold standard scintigraphy in assessing gastrointestinal function

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Search

Database	Pubmed, Embase, Google, Google Scholar, Cochrane, IPA
Search Terms	Ileus, Gastric Motility, Gastric Emptying, Absorption, Pharmacokinetics, Critical Care, Critical Illness, Paracetamol Absorption Test, Acetaminophen Absorption Test, PAT, Acetaminophen, Scintigraphy
Excluded	Absorption test had no comparator
Limits	English, Human
Results	Systematic Review: 1 Clinical Trial: 1

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

How Useful Is Paracetamol Absorption as a Marker of Gastric Emptying?

A Systematic Literature Study

MARLEEN WILLEMS, MD, A. OTTO QUARTERO, MD, PhD,
and MATTIJS E. NUMANS, MD, PhD

Digestive Diseases and Sciences, Vol. 46, No. 10 (October 2001), pp. 2256–2262

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Willems et al.

D	• Searched Medline from 1966 to 1998 • Search terms: acetaminophen, gastric emptying • 13 trials included (N= 180)
P	• 8 trials included healthy volunteers (n=75) • 3 trials included upper GI patients (n=50) • 1 trial included Crohn's/celiac patients (n=41) • 1 trial included convalescent patients (n=14)
I	Paracetamol Absorption Test
C	Scintigraphy
O	Correlation coefficient • Satisfactory ≥ 0.60 • Moderate 0.45 - 0.60 • Poor < 0.45

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Willems et al. Results

Method/Measurement of Comparison to Scintigraphy	# Trials	# Patients	Correlation #Trial (% Patients)		
			Poor	Mod	Sat
Max paracetamol concentration	4	42	2 (40)	-	2 (60)
Area-under-the-plasma-concentration-time-curve	7	115	2 (15)	2 (34)	3 (51)
Fixed-time paracetamol concentrations	4	64	1 (39)	1 (22)	2 (39)
Time to max paracetamol concentration	5	59	2 (32)	-	3 (68)

*trials may be counted twice

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Willems et al. Conclusion

- Using Cmax, Tmax, AUC, the PAT showed satisfactory correlation to scintigraphy

Willems et al. Critique

- Pro
  - Wide variability in age (21-75 yo)
  - Directly compared PAT to gold standard
- Con
  - 42% of patients were healthy volunteers
  - Variable test meals
    - Orange juice, corn flakes, milk, beef
  - Different meal delivery methods
  - Different scintigraphy markers
    - 113m Indium (liquid), 99m Technetium (solid)
  - Did not assess adverse effects of tests
  - No hard outcome measures (eg mortality, GI complications)

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Gastric emptying: a comparison of three methods

HENNING GLERUP[1], HENRIK BLUHME[2], GERDA E. VILLADSEN[3], KARIN RASMUSSEN[2], NIELS EJSKJAER[4] & JENS F. DAHLERUP[5]

Scandinavian Journal of Gastroenterology, 2007; 42: 1182–1186

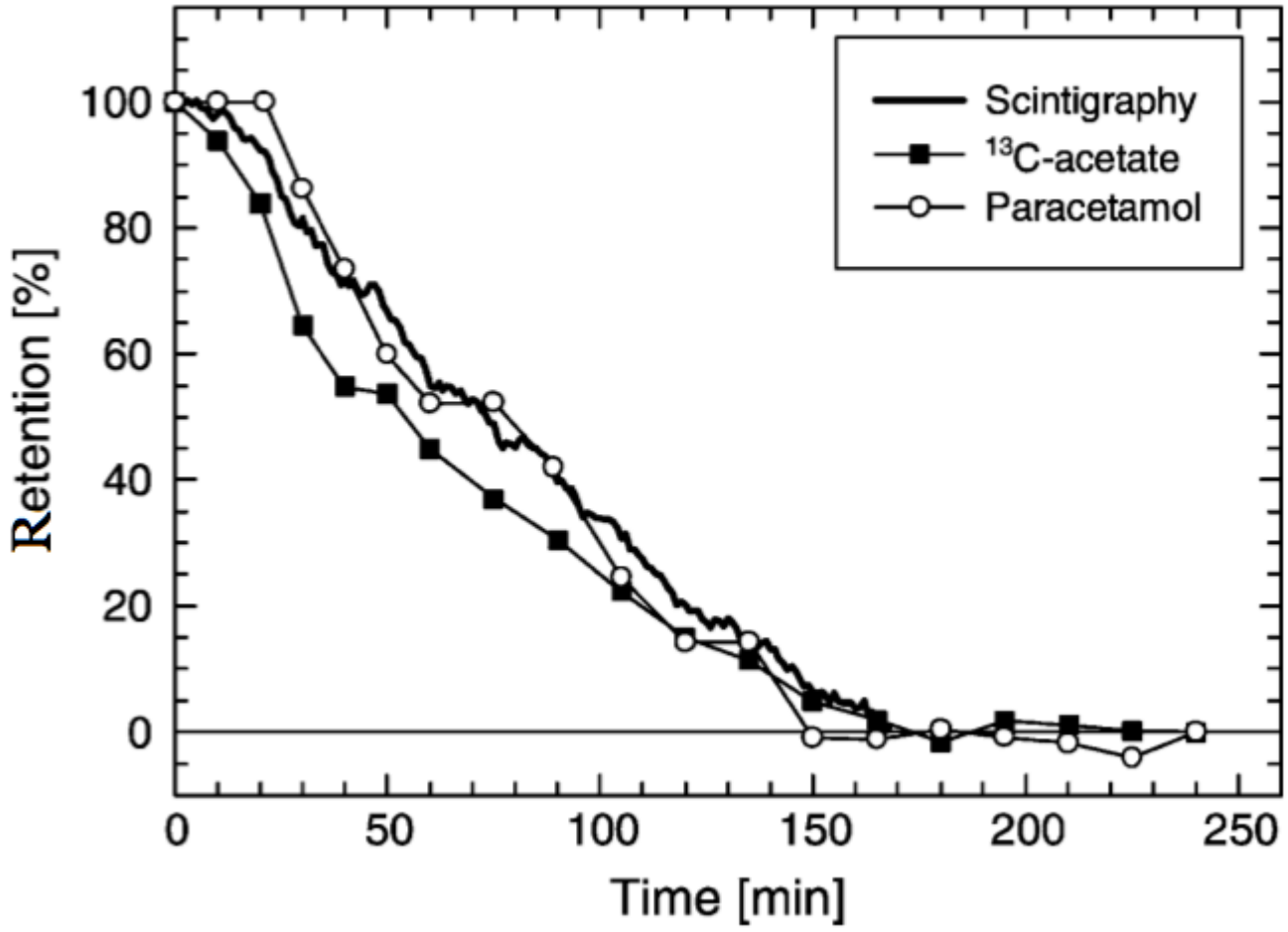
Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Glerup et al.

D	Liquid meal given orally: 44.4g instant milk, 15.6g olive oil, 45.0g glucose + 4mL/kg water containing per mL: 5mg paracetamol, 75mg 13C-natrium acetate, 20 MBq 99m Technesium-Diethylene-Triamine-Penta-Acetate (Tc-DTPA)
P	N=10, healthy volunteers, 5M/5F Age 20-60yo (mean 37.7)
I	Scintigraphy
C	Paracetamol Absorption Test Sampling first 4 patients: 0, Q10min x1h, Q15min x30min, Q30min x2h Last 6 patients: 0, Q10min x1h, Q15min x3h
C	13C breath test Sampling first 4 patients: 0, Q15min x2h, Q30min x2h Last 6 patients: 0, Q10min x1h, Q15min x3h
O	Retention curve comparison of PAT/Breath test to the gold standard scintigraphy

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Glerup et al. Results



Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Scandinavian Journal of Gastroenterology, 2007

Glerup et al. Results

	^{13}C-acetate breath test			Paracetamol absorption test		
Quartile	Mean ΔT (SD) (min)	*t*-test	*p*-value	Mean ΔT (SD) (min)	*t*-test	*p*-value
75%	13.03 (7.67)	5.37	0.0004	0.31 (10.80)	0.09	0.93
50%	18.84 (11.45)	5.21	0.0006	2.02 (14.39)	0.45	0.67
25%*	14.98 (12.10)	3.71	0.0059	−1.80 (15.79)	0.34	0.74

Scandinavian Journal of Gastroenterology, 2007

Glerup et al. Conclusions

- The paracetamol absorption test closely approximated gastric emptying as measured by scintigraphy, more closely than the 13C-breath test

Glerup et al. Critique

- Statistical significance ≠ clinical significance
- Pro:
  - All 3 test performed simultaneously
- Con:
  - Used healthy volunteers with no comorbidities
    - ?applicability to sick patients
  - Used non-standardized meal
  - Meal swallowed, speed not described
  - Did not report adverse effects of tests
  - Did not assess hard outcomes

Summary

PAT

- Non-invasive
- Relatively inexpensive
- No special or additional equipment
- No special technique
- Closely approximates gastric emptying

Scintigraphy

- Non-invasive
- Potentially costly
  - Tracer
  - Gamma-camera
  - Person-hours
- Special equipment
- Nuclear Medicine consult
- Visualize anatomical and physiological GI processes

Critique

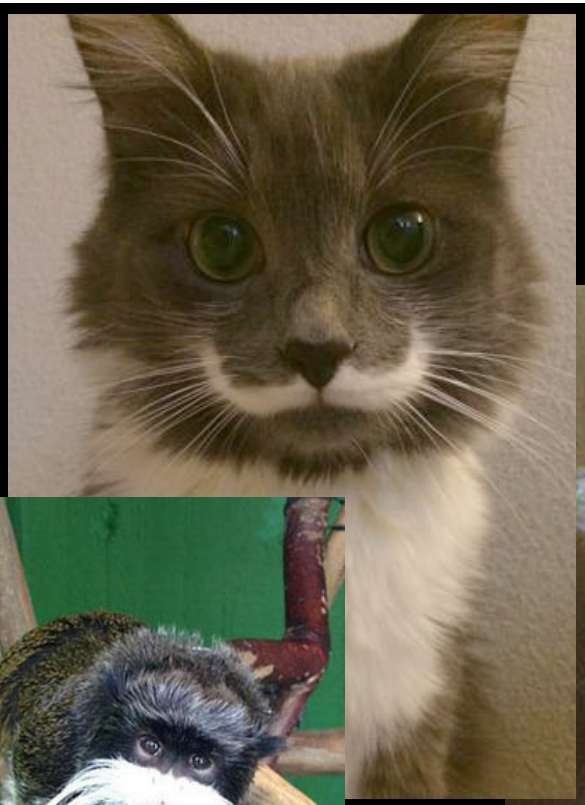
- Assume acetaminophen = analogue
  - Similar absorption
  - Similar physiochemical properties
- Test has potential risk
  - Giving a potentially unnecessary drug
- May not be appropriate in all situations
  - Drug overdose
  - Hepatic(/renal) dysfunction
- Studies not designed to address adverse effects or hard outcomes

When to consider a PAT

- Patient ?GI dysmotility
  - High gastric residuals + vomiting/abdo distension
- Drug level cannot easily be measured
- Must deliver a drug and IV route not available or ideal
  - Medication shortage
  - Parenteral formulation not available (eg clobazam)
  - IV ADE (eg fluid overload, diluent toxicity)

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Questions?



Jonathan Mailm
PharmD Studen

BONUS SLIDES

Suggestions for Conducting PAT

TABLE 2. GUIDELINES AND KEY POINTS FOR STANDARDIZED PARACETAMOL ABSORPTION TEST FOR GASTRIC EMPTYING

Test should be performed after a fast of at least 12 hr
Patients should be off medication that affect motility for 48 hr (eg, prokinetics, anticholinergics, tricyclic antidepressants)
No simultaneous use of drugs during test period
Mixed/liquid meal should be used
Meal composition: 300–500 ml; >300 kcal; 25–30% protein, 15–20% fat, 45–50% carbohydrates
Paracetamol dose: 1.5 g or 20 mg/kg; administered in solution
Fixed position
Age: insufficient evidence
Gender: insufficient evidence
Correlation coefficient: C_{max}: accurate, repetitive blood sampling required; AUC: highest correlation coefficient, very accurate, long test period, complicated calculation; $C(2t)/C(t)$: easy, reliable, short test period, little experience

Digestive Diseases and Sciences 2001

Ensure drug clearance/levels affected by condition

- Atorvastatin in Sepsis
  - N= 35
  - Adult patients
  - With/without sepsis
  - CCU, ICU level 1 & 2, Ward, Healthy
  - If high gastric residuals, feeds were held but dose was given

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Kruger et al. Intensive Care Med 2009;35:717–721

Atorvastatin (cont)

- All groups had higher serum levels than healthy controls
- Confounders:
  - Atrovastatin may have higher levels in sepsis / illness
  - Did not tell us how many (or who) had high gastric residuals
    - We know up to 60% of ICU patients have dysmotility

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Kruger et al. Intensive Care Med 2009;35:717–721

Other Markers of GI intolerance

- Vomiting
- Abdominal distension
- Aspiration
- Diarrhea

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Ahkee et al. *Pharmacotherapy* 1997;17(3):569-575
Acosta-Escribano et al. *Int Care Med* 2010;36:1532–1539

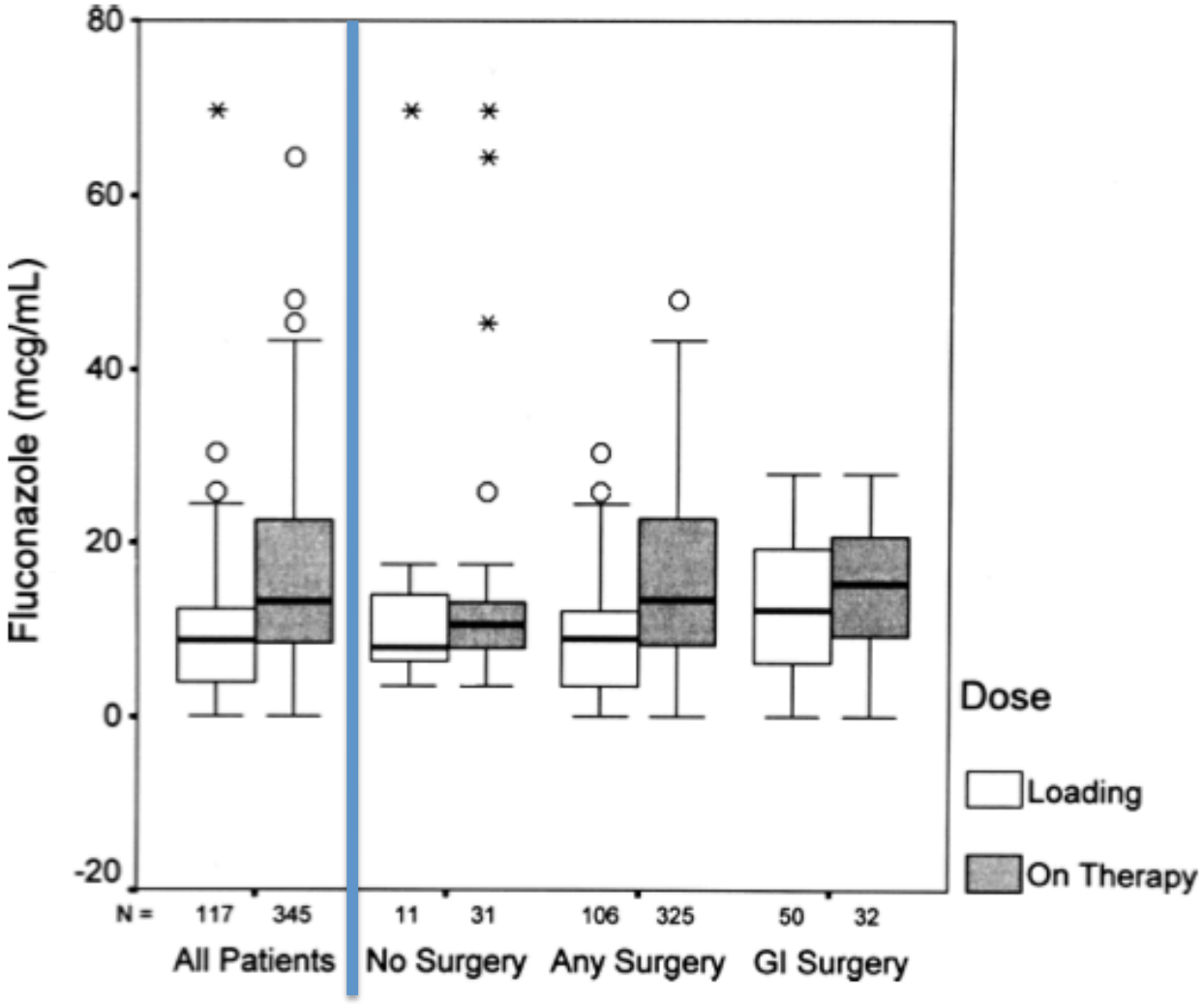
Oral Fluconazole

- PO fluconazole in critically ill for prophylaxis
  - n= 121, Mixed ICU population
    - No surgery, any surgery, GI surgery
  - 800 mg load then renally adjust maintenance dose MWF, levels drawn immediately before dose
  - Drug given regardless of post-op status/feed tolerance
  - Dose administered via NG tube, flushed 30 mL water, clamped for 1 hour
- No significant difference in levels between patients

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Pelz et al. Surgery 2002;131:534-40

Serum Fluconazole Level



Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Pelz et al. Surgery 2002;131:534-40

Confirm NJ Placement → PAT

- Mixed Adult ICU
- N = 32
  - Gastric = 17
  - Jejunal = 16
- Acetaminophen 15mg/kg
- Avoid second Abdominal X-ray
- Compared NG to NJ administration
  - Shorter Tmax, larger Cmax for acetaminophen

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Berger et al. JPEN 2003;27:151-155

High Gastric Residuals → PAT

- Adult, mixed ICU
- N = 32
- PAT test if gastric residual > 150 mL or twice hourly rate
- If AUC60 >600 mg*min/L
  - Feeds restarted at same rate
  - All patients tolerated feeds (n = 8)
  - But results took an average of 4 hours

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Cohen et al. Clin Nutr. 2000;19:233–236

Post-Pylorus Administration

- Less overall infections
- Able to deliver more nutrition
  - Achieve goal nutrition more often
  - Patients not tolerating NG have greater chance tolerating NJ administration
    - Gastric stasis, vomiting, aspiration
- Fewer "other" GI complications
  - Distension, vomiting, diarrhea, aspiration, ↑GRV

Jonathan Mailman, BSc(Pharm), ACPR
PharmD Student

Acosta-Escribano et al. Int Care Med 2010;36:1532–1539
Davies et al. Crit Care Med 2002;30:586 –590
Berger et al. Crit Care Med 2000; 28:2217–2223
Boulton-Jones et al. Clin Nutr 2004;23:35–41