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In Reply:—Anderson and Holford disagree with the values for Vd/f that we estimated for rectally administered acetaminophen. To support their claim, they cite two values for the relative bioavailability of rectal *versus* oral acetaminophen:

1. They claim that "bioavailability of rectal compared to oral acetaminophen formulations has been reported as 0.52 (range, 0.24-0.98)," referring to a manuscript by Montgomery *et al.*[1] Unfortunately, those data were not obtained by Montgomery *et al.* but are reported in those authors' introduction as the results of "an unpublished adult study," in which a SmithKline Beecham preparation (rather than the Upsher-Smith preparation used in our study) was examined. We question the relevance of a study performed in adults, the citation of "unpublished data," whose accuracy cannot be verified, and data from a different preparation.
2. They cite a rectal-oral bioavailability ratio of 0.3. This is based on a study in which acetaminophen concentrations peaked at 3 h after rectal administration, yet the final (of four) samples was obtained at 4 h.[2] It is likely that those investigators underestimated the area under the plasma concentration *versus* time curve, thereby underestimating the relative bioavailability of rectally administered acetaminophen.

Anderson and Holford simulate plasma acetaminophen concentrations that might occur with a 20 mg/kg rectal dose. We agree that the mean concentrations observed with this dose do not overlie the simulated values. However, figure 2 in our manuscript demonstrates that mean concentrations for the three doses differ and that our 10-mg/kg dose yields a peak concentration of 4.0 μg/ml at approximately 200 min and that our 30-mg/kg dose (normalized to a dose of 10 mg/kg) yields a peak concentration of 3.7 μg/ml at approximately 220 min.[3] These times-to-peak concentration are consistent with Anderson and Holford's simulations. Doubling these peak concentrations (to predict the peak concentration attained with a 20-mg/kg dose) yields values of 8.0 and 7.4 μg/ml, slightly less than the values predicted by Anderson and Holford's simulations. This difference is expected in that concentrations for each patient should peak at different times so that the average concentration at the median peak time should be less than the average of the individual peak concentrations (fig. 1). Note also that Anderson and Holford use only our most discrepant data (the data from the 20-mg/kg dose) to criticize our model.

Anderson and Holford agree with our claim that suppository size may affect absorption characteristics but are concerned that there is no consistent pattern in the dissolution times. We agree and note in our manuscript that additional studies are needed to determine "factors influencing differences in dissolution." Our model was developed because, with the traditional first-order adsorption model, we observed that "the pharmacokinetics of acetaminophen varied as a function of the dose administered as smaller- . . . *versus* larger-dose suppositories." Allowing for a more complex absorption model markedly improved the quality of the fit. Readers are referred to our manuscript for additional detail.

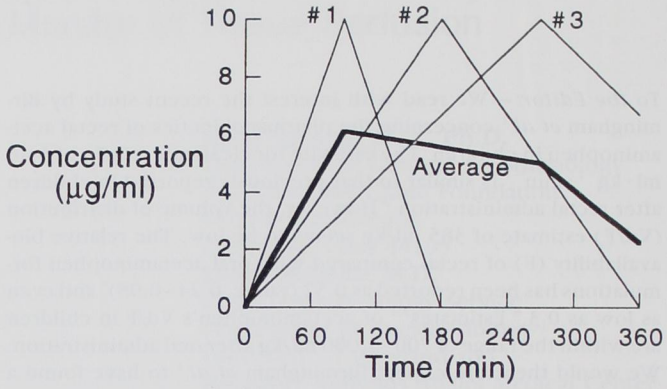

Fig. 1. Theoretical concentrations for three subjects (#1, #2, #3) given acetaminophen rectally are shown. Each thin line represents values for an individual subject; the thick line is the average of the values for the three individuals. If the curves peaked simultaneously, the mean of the peak concentrations would equal the peak of the mean concentrations. However, the peak of the average curve is less than the average of the peak of each of the individual curves, a result of each curve peaking at a different time.

In their pharmacokinetic analysis of rectally administered acetaminophen, Anderson *et al.*[4] used the traditional first-order absorption model. Unfortunately, their manuscript provides no graphics that demonstrate whether their absorption model fits the early plasma concentration data. In addition, their first sample was obtained 1 h after drug administration (whereas our first sample was obtained at 30 min), limiting their ability to determine whether their absorption model fit the plasma concentrations that occurred during the initial absorption phase. If they do not look, they will never know if their pharmacokinetic model misspecifies the early absorption phase.

In summary, we appreciate Anderson and Holford's interest in our analysis. However, we contend that their simulations are compared selectively, rather than with our entire dataset. In addition, their claim about relative bioavailability of rectal *versus* oral preparations of acetaminophen is based on questionable data.

Dennis M. Fisher, M.D.
Professor of Anesthesia and Pediatrics
University of California
San Francisco, California 94143-0648
Patrick K. Birmingham, M.D.
Assistant Professor of Anesthesiology
Charles J. Coté, M.D.
Professor of Anesthesiology and Pediatrics
Northwestern University Medical School
Children's Memorial Hospital
Chicago, Illinois 60614

References

1. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP: Plasma concentrations after high-dose (45 mg · kg^{-1}) rectal acetaminophen in children. Can J Anaesth 1995; 42:982–6

2. Dange SV, Shah KU, Deshpande AS, Shrotri DS: Bioavailability of acetaminophen after rectal administration. Indian Pediatr 1987; 24:331–2

3. Birmingham PK, Tobin MJ, Henthorn TK, Fisher DM, Berkelhamer MC, Smith FA, Fanta KB, Coté CJ: Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: An old drug with new recommendations. ANESTHESIOLOGY 1997; 87:244–52

4. Anderson BJ, Woolard GA, Holford NH: Pharmacokinetics of rectal paracetamol after major surgery in children. Paediatr Anaesth 1995; 5:237–42

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Endoscopic Saphenous Vein Harvesting and $ETCO_2$ in Cardiac Surgery Patients

To the Editor:—Harvest of the greater saphenous vein is a commonly performed procedure in patients undergoing coronary artery bypass grafting (CABG). Minimally invasive video-assisted removal of the saphenous vein in these patients is believed to be associated with decreased complications and greater patient satisfaction than with traditional harvesting techniques.[1–3]

A new endoscopic vein harvesting system (Guidant Corporation, Menlo Park, CA) uses carbon dioxide (CO_2) to aid in the visualization and dissection of the saphenous vein along its linear course. CO_2 is insufflated at 12–15 mmHg/min, and 10–20 l of CO_2 may be insufflated during this 45- to 60-min procedure.

Increases in minute ventilation required to maintain preinsufflation arterial carbon dioxide tension ($PaCO_2$) during laparoscopic cholecystectomy have been reported.[4–6] We have observed a 10–20% increase in the baseline end tidal carbon dioxide ($ETCO_2$) levels, as measured by capnography, in patients undergoing endoscopic saphenous vein harvesting with CO_2 insufflation. However, early in the learning curve, greater total amounts of CO_2 are insufflated because of increased time needed to master the dissection process. Hence, we have observed even greater increases in $ETCO_2$.

At our institution, concomitant with saphenous vein dissection, the Internal Mammary Artery (IMA) is being exposed by the cardiac surgeon. We routinely decrease the patient's tidal volume (TV) during this time to assist the surgeon in his or her visualization of the IMA. Increases in the $ETCO_2$ from this decrease in TV compounded by the increase in $ETCO_2$ resulting from the endoscopic saphenous vein harvest may lead to notable changes in $ETCO_2$ and alterations in hemodynamics. If video-assisted endoscopic saphenous vein harvest becomes routine in CABG surgery, precautionary measures (such as increases in respiratory rate) should be anticipated.

James M. Gayes, M.D.
Department of Anesthesiology
Abbott Northwestern Hospital
Chicago Avenue at 28th Street
Minneapolis, Minnesota 55404

References

1. Allen KB, Shaar CJ: Endoscopic saphenous vein harvesting. Ann Thor Surg 1997; 64(1):265–6

2. Cusimano RJ, Dale L, Butnay JW: Minimally invasive surgery for the removal of the greater saphenous vein. Can J Surg 1996; 39:386–8

3. Lumsden AB, Eaves FF 3rd, Ofenloch JC, Jordan WD: Subcutaneous, video-assisted saphenous vein harvest: A report of the first 30 cases. Cardiovasc Surg 1996; 4(6):771–6

4. Baraka A, Jabbour S, Aouad M, Najjar F, Khoury G, Sibai A: Can pulse oximetry and end-tidal capnography reflect arterial oxygenation and carbon dioxide elimination during laparoscopic cholecystectomy? Surg Laparosc Endosc 1994; 4(5):353–6

5. Baraka A, Jabbour S, Aouad M, Najjar F, Khoury G, Sibai A: End-tidal carbon dioxide tension during laparoscopic cholecystomy. Correlation with baseline value prior to CO_2 insufflation. Anaesthesia 1994; 49(4):304–6

6. Wahba RW, Mamazza J: Ventilatory requirements during laparoscopic cholecystectomy. Can J Anaesth 1993; 40(3):206–10

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