or cardiovascular death, so it would have been more appropriate to refer to a reduction in the incidence of myocardial infarction, as opposed to cardiovascular events.

Our third issue of concern relates to the data for myocardial infarction, which was 1 of 3 outcomes measured in the study. The authors reported a 0.6% reduction in this outcome among patients assigned to receive double-dose clopidogrel, relative to those receiving the standard dose. There are 2 reasons why we question the clinical importance of this result. First, the effect size was small and of debatable clinical importance. Second, it is possible that this finding is a false positive (type 1 error), as no *p* value adjustment was made for the multiple comparisons performed in the trial.[4] The authors also used a postrandomization subgroup of the overall trial population, which leads to additional risk of a type 1 error.[5]

Our fourth issue of concern is the lack of reporting of harm in the conclusion statements of the abstract and the full article, which might lead a reader to believe that there are no risks associated with the double-dose regimen. In fact, the incidence of major bleeding (as defined by the CURRENT-OASIS 7 authors) was higher in the double-dose group than the standard-dose group (1.6% versus 1.1%, hazard ratio 1.41, 95% confidence interval 1.09–1.83, $p = 0.009$).[2] This represents a 0.5% absolute increase in the hazard of harm (major bleeding). The omission of this information from the concluding statements appears to be selective reporting, which is misleading.

Our final issue of concern relates to the overall assessment of harm versus benefit. Specifically, the 0.6% reduction in risk of myocardial infarction would seem to be nullified by the 0.5% increase in the risk of major bleeding. Although some would argue that the benefit of preventing myocardial infarction outweighs the risk of a major bleeding event, these 2 outcomes are only a subset of the possible effects of the double-dose regimen. Returning to our first issue of concern, described above, a full analysis of serious adverse events could help in determining the net effect of the double-dose regimen and provide more confidence in saying whether the benefit outweighs the risk.

Does this study provide enough information to support a double-dose regimen of clopidogrel? We're not convinced. Does something need to be done about the selective reporting of harm in conclusion statements? Absolutely.

References

1. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;363(10):930-942. Erratum in: *N Engl J Med* 2010;363(16):1585.
2. Mehta SR, Tanguay J, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, et al.; CURRENT-OASIS 7 Trial Investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010;376(9748):1233-1243.
3. Serious adverse event analysis: lipid-lowering therapy revisited. *Therapeutics Letter 42*. Vancouver (BC): Therapeutics Initiative; 2001. Available from: www.ti.ubc.ca/newsletter/serious-adverse-event-analysis-lipid-lowering-therapy-revisited
4. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC Med Res Methodol* 2002;2:8.
5. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117. doi:10.1135/bmj.c117.

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Pediatric Pharmacokinetics of Vancomycin: A Canadian Perspective

The practice of monitoring serum vancomycin concentrations in children remains controversial because of pharmacokinetic variability within and between patients and a lack of guidance from the literature.[1-8] Two questions remain unanswered: Should we be measuring the level of this drug in children, and what therapeutic ranges should be targeted?[1]

At the time of writing (late 2010), the initial vancomycin dosage at the Centre hospitalier universitaire (CHU) Sainte-Justine in Montréal, Quebec, ranged from 10 to 15 mg/kg per dose every 6 or 8 h, with each dose administered slowly by infusion over 1 h. For all patients, trough and peak vancomycin levels are usually measured in association with the third or fourth dose, with the trough being determined immediately before administration and the peak 1 h after infusion is complete. The dosage is then adjusted to achieve the target therapeutic ranges (i.e., 5–10 µg/mL for the trough and 20–40 µg/mL for the peak), according to the pharmacist's recommendations, which are based on a one-compartment model (Sawchuk–Zaske method) and calculated pharmacokinetic parameters. A local retrospective drug utilization review of vancomycin was conducted in 2010, using data for 30 patients with 5 days or more of therapy. Measured serum concentrations for trough and peak fell within the specified therapeutic ranges in 60% and 33% of the cases, respectively, up to the fifth day of vancomycin treatment (Delicourt A, Lavoie A, Touzin K, Therrien R, Lebel D. A retrospective study of vancomycin therapeutic drug monitoring in pediatrics. Manuscript submitted for publication).

To characterize therapeutic drug monitoring practices for vancomycin in pediatric patients across Canada, we surveyed 13 Canadian pediatric centres in May 2010 using SurveyMonkey. The questionnaire was to be completed by a single clinical pharmacist at each hospital, on the basis of the person's opinion and pursuant to the centre's usual practice. Data related to neonatology were excluded. Twelve of the 13 centres responded, for a response rate of 92%.

The initial vancomycin dosage used for children varied among the respondents, and the majority of children received the drug every 6 h (Table 1). Eight of the 12 respondents reported that their hospitals did not have a maximum initial dose. Among the remaining hospitals, the maximum dose was 60 mg/kg per day at 3 centres and 100 mg/kg per day at 1 centre.

After dose adjustment, a new target trough, with or without measurement of peak levels, was prescribed for a median of 80% (range 30% to 95%) of patients at each hospital ($n = 9$ respondents). Trough level was measured for a median of 100% (range

Table 1. Initial Vancomycin Dosages and Intervals Used for Pediatric Care in Canada

Dosage Characteristic	Age Group; Estimated % of Patients (Median and Range)			
	< 1 Year* (*n* = 12 Hospitals)		≥ 1 Year (*n* = 12 Hospitals)	
Weight-based dose				
< 10 mg/kg per dose	0	(0–5)	0	(0–5)
10 mg/kg per dose	50	(0–100)	58	(0–80)
15 mg/kg per dose	45	(0–80)	30	(20–70)
> 15 mg/kg per dose	0	(0–70)	0	(0–70)
Dosing interval				
4 h	0	(0–5)	0	(0–0)
6 h	73	(30–100)	80	(30–100)
8 h	18	(0–70)	18	(0–70)
12 h	0	(0–10)	0	(0–10)
Continuous infusion	0	(0–0)	0	(0–10)

*Excluding neonates.

50% to 100%) of patients at each hospital (*n* = 11 respondents), and peak level was measured for a median of 10% (range 0% to 100%) of patients (*n* = 12 respondents). Of the 12 centres surveyed, 7 reported that they measured peak levels in fewer than 10% of patients.

Although some authors believe that the controversy regarding therapeutic monitoring for vancomycin is over, the results of this survey indicate that pediatric practice varies widely across Canada. Vancomycin is a time-dependent antibiotic. As such, to ensure efficacy, its concentration at the site of action must be maintained, between consecutive doses, at a level higher than the minimum inhibitory concentration. In addition, the relation between toxicity and maximum serum concentration has not been clearly demonstrated.[9] Although there are few conclusive data on the superiority of one method over another (i.e., monitoring of peak and trough levels versus monitoring trough levels only), a majority of children receiving vancomycin therapy do not have samples drawn for monitoring of peak levels. In answer to the questions that we posed at the beginning of this letter, we believe that monitoring of peak levels should be limited to life-threatening situations (e.g., meningitis) and patients with altered volume of distribution. Also, the targeted therapeutic range for the trough should be 5 to 15 mg/mL.

More generally, clinicians should balance their actions between efficiency and safety and should periodically reconsider their practice. Such evaluation of clinical practice should include periodic review of the literature, local drug utilization reviews, and benchmarking. Revised guidelines for vancomycin monitoring (i.e., 15 mg/kg per dose in most clinical situations, with monitoring of peak levels limited to exceptions) were adopted by our pharmacy and therapeutics committee, and practice will be monitored over the next 12 months.

References

1. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009;66(1):82-98. Erratum in: *Am J Health Syst Pharm* 2009;66(10):887.
2. Seay RE, Brundage RC, Jensen PD, Schilling CG, Edgren BE. Population pharmacokinetics of vancomycin in neonates. *Clin Pharmacol Ther* 1994;56(2):169–175. Erratum in: *Clin Pharmacol Ther* 1995;58(2):142.
3. Tan WH, Brown N, Kelsall AW, McClure RJ. Dose regimen for vancomycin not needing serum peak levels? *Arch Dis Child Fetal Neonatal Ed* 2002;87(3):F214–F216.
4. Glover ML, Cole E, Wolfsdorf J. Vancomycin dosage requirements among pediatric intensive care unit patients with normal renal function. *J Crit Care* 2000;15(1):1-4.
5. de Hoog M, Schoemaker RC, Mouton JW, van der Anker JN. Vancomycin population pharmacokinetics in neonates. *Clin Pharmacol Ther* 2000;67(4):360-367.
6. Jimenez-Truque N, Thomsen I, Saye E, Creech CB. Should higher vancomycin trough levels be targeted for invasive community-acquired methicillin-resistant *Staphylococcus aureus* infections in children? *Pediatr Infect Dis J* 2010;29(4):368-370.
7. Crumby T, Rinehart E, Carby MC, Kuhl D, Talati AJ. Pharmacokinetic comparison of nomogram-based and individualized vancomycin regimens in neonates. *Am J Health Syst Pharm* 2009;66(2):149-153.
8. Taketomo CK, Hodding JH, Kraus DM. *Pediatric dosage handbook*. 16th ed. Hudson (OH): Lexi-Comp Inc; 2009.
9. Miles MV, Li L, Lakkis H, Youngblood J, McGinnis P. Special considerations for monitoring vancomycin concentrations in pediatric patients. *Ther Drug Monit* 1997;19(3):265-270.

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