Effective analgesia after cesarean delivery needs pharmacokinetic input

Sir,

We read the paper presented by Ismail *et al.* with great interest.[1] In a cohort of 263 women following cesarean delivery, the authors documented that the pain management protocol was used in a clinical setting, and was adequate in terms of safety. Unfortunately, the protocol was inadequate in terms of efficacy [< 3/10 visual analog scale (VAS) score at rest and movement].[1] Besides, the general advantages of adequate postoperative analgesia in patients who had a cesarean delivery has some population specific aims. These are related to the risk for thromboembolic events which can be precipitated by immobility. Furthermore, opioid induced sedation should be avoided to facilitate mother-child interaction. Finally, transfer of sedative compounds like opioids to the newborn through breastfeeding also should be avoided.

When paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are used, we can decrease the opioid consumption, and thus indirectly reduce the opioid side effects. Preventive analgesia using non-opioid analgesic strategies is thus a pathway to reduce the postoperative pain while minimizing the risks for mother and newborn. This is also what the authors aimed for by using diclofenac, paracetamol or both.[1,2]

Although this practice is common throughout the world, we noticed that the doses used are mainly '*eminence based*' rather than 'evidence based,' and not adapted to pregnancy related changes in pharmacokinetics. During pregnancy, there are changes in body fluid distribution volume, mainly due to changes in the body composition, metabolic activity affecting the drug metabolism, and in renal clearance.[3] In essence, pregnancy warrants a tailored approach since these alterations in physiology affect the drug disposition. Despite these changes in drug disposition, even commonly administered drugs like non-opioid analgesics have not been properly evaluated regarding their pharmacokinetics during pregnancy.[3]

Since this journal focuses on the link between anesthesiology and clinical pharmacology, we wanted to inform the readers about our ongoing research on non-opioids pharmacokinetics (PK) at delivery, and thus wanted to illustrate the impact of paracetamol disposition on pregnancy as a proof of relevance.[2]

Clearance (L/h) after intravenous paracetamol (2 g) loading dose administration in 28 women following cesarean delivery was significantly higher when compared to a similar dataset in 14 healthy female volunteers (median estimates 20.3 vs 15.5 L/h, Figure 1).[2,4] Differences remained significant ($P < 0.05$) after correction for pregnancy related changes in the body surface area, reflecting the fact that drug metabolism is increased during pregnancy. More recently, a similar PK study on intravenous ketorolac has been finalized (www.clinicaltrials.gov, NCT01291472).

Although the relation between plasma concentration and analgesia has not been fully described, and despite the fact that post cesarean pain also relates to pharmacodynamic covariates such as thepresence of labor, duration of surgery and individual pain thresholds,[2] we claim that these observations illustrate the need for integrated pharmacodynamics/pharmacokinetic

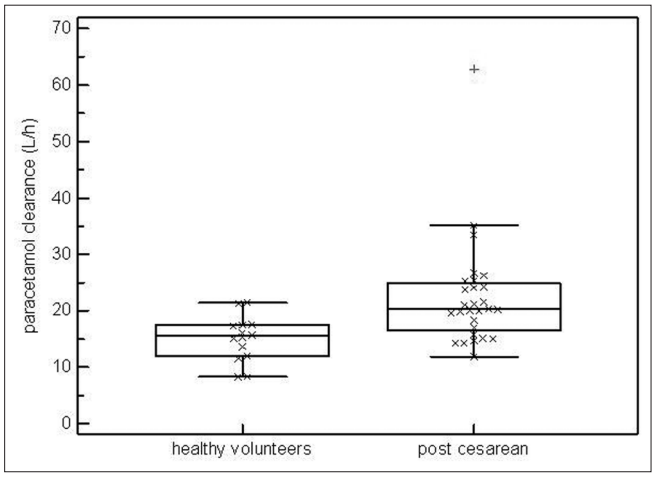

Figure 1: Individual paracetamol clearance estimates in 28 patients post cesarean delivery[2] and in 14 healthy female volunteers.[4]

studies in the field of peripartum analgesia. Referring to the recently published survey on drugs administered for pain, nausea or pruritus after cesarean delivery, we encourage caregivers to consider similar efforts for other compounds, since it is unlikely that the impact of pregnancy on pharmacokinetic is limited to non-opioid analgesics.[2,5]

Acknowlegdements

Aida Kulo was supported by a Join EU-SEE scholarship, Karel Allegaert by the Fund for Scientific Research, Flanders (Fundamental Clinical Investigatorship 1800209N).

Aida Kulo[1,2], Jan de Hoon[1], Nedzad Mulabegovic[2], Karel Allegaert[3]

[1]Center for Clinical Pharmacology, [3]Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium, [2]Institute of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Sarajevo, Sarajevo, Bosnia Herzegovina

Address for correspondence: Dr. Karel Allegaert, Neonatal Intensive Care Unit, University Hospital, Herestraat 49, 3000 Leuven, Belgium.
E-mail: karel.allegaert@uzleuven.be

References

1. Ismail S, Shahzad K, Shafiq F. Observational study to assess the effectiveness of postoperative pain management of patients undergoing elective cesarean section. J Anaesthesiol Clin Pharmacol 2012;28:36-40.
2. Kulo A, van de Velde M, de Hoon J, Verbesselt R, Devlieger R, Deprest J, *et al.* Pharmacokinetics of a loading dose of intravenous paracetamol post caesarean delivery. Int J Obstet Anaesth 2012;21:125-8.
3. Feghali MN, Mattison DR. Clinical therapeutics during pregnancy. J Biomed Biotechnol 2011;2011:783528.
4. Gregoire N, Hovsepian L, Gualano V, Evene E, Dufour G, Gendron A. Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. Clin Pharmacol Ther 2007;81:401-5.
5. Marcus HE, Fabian A, Dagtekin O, Schier R, Krep H, Böttiger BW, *et al.* Pain, postdural puncture headache, nausea, and pruritus after cesarean delivery: a survey of prophylaxis and treatment. Minerva Anestesiol 2011;77:1043-9.

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.98375