In Response

Paliwhal et al[1] questioned the ideal time for pupillary dilation reflex (PDR) assessment. We conducted a pragmatic trial[2] and chose subsequently to record the PDR at the end of the surgery for 2 main reasons. First, opioid-induced pupillary constriction is known to diminish the PDR.[3] It is thus not possible to exclude a measurement bias immediately after the induction of the general anesthesia, unless after several minutes of opioid discontinuation. Indeed, in an unpublished preliminary study including 40 patients, we recorded the PDR before the beginning of the surgery, with remifentanil discontinuation immediately on anesthesia induction. We found that patients had a median (standard deviation) remifentanil effect-site concentration of 1.4 ng·mL^{-1} (0.8) with only a small difference in PDR between the blocked side (median [interquartile range] PDR of 4% [2–14]) and the control side (11% [2–19]), P = .14. The range of these results is closer to the one described by Isnardon et al[4] (PDR between 4% and 17%) than to our results in which the effect-site concentration approached 0 ng·mL^{-1} (PDR between 9% and 41%). Second, in our study,[2] the delay between the realization of the thoracic paravertebral nerve block and the surgery could be <15 minutes, far inferior to the time delay needed to attain the maximal effect of the ropivacaine. Indeed, the mean (standard deviation) time from injection to maximal ropivacaine-induced effect on current perception threshold is 22 (13) minutes in femoral nerve block.[5] Using only ropivacaine, one should probably wait between 30 and 40 minutes before assessing the block with the PDR, which is not compatible with a pragmatic trial. Isnardon et al[4] added lidocaine to ropivacaine, leading to a shorter action delay likely required for an early assessment of a peripheral nerve block with the PDR.

Last, even if the strength of the stimulus was higher on the operated and blocked side, it did not prevent the PDR from being lower after stimulation of the operated and blocked side. The tetanic stimulation used (60 mA, 100 Hz) may be far superior to usual postoperative pain and not additive with it.

In short, one can evaluate the PDR before the surgery for a similar stimulus on both sides but should be cautious regarding the amount of opioid and the pharmacodynamics of the local anesthetic used.

Baptiste Duceau, MD
Christian Jayr, MD, PhD
Institut Curie
Department of Anesthesiology
Hôpital René Huguenin
Saint-Cloud, France
bduceau@gmail.com

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Renal Interstitial Exhaustion and SGLT2 Blockers

To the Editor

Sodium–glucose cotransporter-2 inhibitors (SGLT2is) are recently in focus of both researchers and clinicians as they act uniquely through increasing renal glucose excretion which is independent of insulin. Potential perioperative hazards of SGLT2i have been thoroughly discussed by Peacock et al.[1] In addition, the following concerns might also be taken into consideration.

Proximal tubule of the kidney is considered as the main site of SGLT2i action wherein sodium-coupled glucose reabsorption is blocked significantly. The consequent increase in sodium delivery to distal tubule, however, imposes undesirable workload and energy expenditure in macula densa which in turn leads to further adenosine triphosphate breakdown, adenosine monophosphate generation, and stimulation of adenosine type-1 receptors in afferent arteries. The latter is accompanied by afferent arterial vasoconstriction and subsequent decrease in intraglomerular pressure. Yet, SGLT2 inhibitory impact is not the same on all glomeruli: more perfused glomeruli with more distal glucose and sodium chloride delivery are more prone to afferent arterial vasoconstriction, and consequently, more vulnerable glomeruli are further protected against hyperfiltration. Meanwhile, the increased workload on distal nephrons creates interstitial hypoxemia which in turn makes the kidney vulnerable to other predisposing factors such as nonsteroidal anti-inflammatory drug (NSAID) nephropathy, ischemic nephropathy, radio contrast nephropathy, and hypoperfusion.[2] Therefore, further precautions should be taken into account in these groups of patients.

Moreover, SGLT2 inhibition is associated with a modest activation of the renin–angiotensin–aldosterone system. Therefore, combination of a renin–angiotensin–aldosterone system and SGLT2i, through dilation of efferent arterioles, creates much more intraglomerular pressure decrement and deteriorates the already compromised condition.[3] Interestingly, some SGLTis such as canagliflozin have a mixed SGLT2 and SGLT1 inhibitory properties; SGLT1 expression increases following tissue ischemia and its inhibition attenuates the oxidative stress in ischemic tissues.[4]

Mohammadreza Ardalan, MD
Kidney Research Center
Tabriz University of Medical Sciences
Tabriz, Iran

Samad E. J. Golzari, MD
Research Center for Evidence Based Medicine
Tabriz University of Medical Sciences
Tabriz, Iran
dr.golzari@hotmail.com

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In Response

We thank Drs Ardalan and Golzari[1] for their commentary about our manuscript related to sodium–glucose cotransporter-2 (SGLT2) inhibitors in the perioperative setting.[2] As outlined by them, increased sodium delivery to the macula densa through SGLT2 inhibition is associated with afferent arteriolar vasoconstriction leading to decreased glomerular hypertension and hyperfiltration, albuminuria, and an attenuated risk of diabetic kidney disease progression in type 2 diabetes.[3–5] In addition to these renoprotective effects, SGLT2 inhibition reduces cardiovascular risk in patients with type 2 diabetes in cardiovascular safety trials.[5,6] Moreover, in the Empagliflozin, Cardiovascular Outcomes, and Mortality in type 2 diabetes (EMPA-REG OUTCOME) and Canagliflozin Cardiovascular Assessment Study (CANVAS) Program trials, SGLT2 inhibition was not associated with an increased risk for acute kidney injury and was in fact significantly lower with empagliflozin versus placebo in EMPA-REG OUTCOME. Other safety concerns that emerged with canagliflozin from the CANVAS Program, including an increase in the risks of amputation and fracture, have been extensively discussed elsewhere.[7] Despite salutary cardiorenal effects and an overall favorable side effect profile, it is important to note that these cardiovascular safety trials were not designed to assess perioperative risk, nor were they intended to assess the potential for adverse effects in other specific clinical situations, such as in the context of radiocontrast studies or NSAID (nonsteroidal anti-inflammatory drug) use. In real-world data, SGLT2 inhibitors have variably been reported to have protective, neutral, and deleterious effects on kidney injury risk.[8–10]

Accordingly, due to both uncertainty around renal risk, particularly in high-risk individuals in clinical conditions associated with reduced renal perfusion and/or hypoxia in the renal parenchyma,[11] SGLT2 inhibitors should be held during acute illness, in the perioperative phase and in clinical situations that may impact glomerular filtration rate (eg, exposure to contrast or nephrotoxic medications including NSAIDs), at least until more data are available.[2] As highlighted in the Diabetes Canada Clinical Practice Guidelines and reviewed in our manuscript, SGLT2 inhibitors have been added to the list medications, which should be temporarily held on "sick days," including perioperatively.[12] A relatively complete list of other medication classes that should be similarly discontinued during these sick day periods can be recalled using the mnemonic *S*-sulfonylureas, *A*-angiotensin converting enzyme inhibitors, *D*-diuretics, direct renin inhibitors, *M*-metformin, *A*-angiotensin receptor blockers, *N*-nonsteroidal anti-inflammatory, *S*-SGLT2 inhibitors (Diabetes Canada Clinical Practice Guidelines Appendix 7 [2015]). In taking this approach, patients may maximize the chance of deriving benefits from chronic use of SGLT2 inhibitors while mitigating risk associated with acute changes in systemic effective circulating volume status.

Sharon C. Peacock, BSc (PT), MD
Department of Anesthesiology
University of Toronto
Toronto, Ontario, Canada
Julie A. Lovshin, MD, PhD
Division of Endocrinology
Department of Medicine
Sunnybrook Health Science Centre
University of Toronto
Toronto, Ontario, Canada
Department of Physiology
Banting and Best Diabetes Centre
University of Toronto
Toronto, Ontario, Canada
David Z. I. Cherney, MD, PhD
Division of Nephrology
Department of Medicine
Toronto General Hospital
Toronto, Ontario, Canada
Department of Physiology
Banting and Best Diabetes Centre
University of Toronto
Toronto, Ontario, Canada

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