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CORRESPONDENCE

Non-opioid analgesic use and concerns for impaired organ protection

Y. Wu[1,2], H. M. Heymann[1] and E. R. Gross[1,*]

[1]Department of Anesthesiology, Perioperative and Pain Medicine, School of Medicine, Stanford University, Stanford, CA, USA and [2]Department of Anesthesiology, Second Affiliated Hospital of Anhui Medical University, Hefei, China

*Corresponding author. E-mail: ergross@stanford.edu.

Editor—With increasing use of non-opioid therapies for intra- and postoperative pain control, the shortcomings of using multimodal analgesic therapies to minimize opioid use need consideration. In particular, understanding how non-opioid analgesics influence organ protection must be assessed prior to changing practice to opioid-sparing modalities. For example, a randomized double-blind study reported an increased incidence of cardiovascular complications when cyclooxygenase-2 (COX-2) inhibitors were used post-operatively after coronary artery bypass grafting.[1] Further, the European Medicines Agency identifies that COX-2 inhibitor use is contraindicated for those with known cardiovascular disease.

Thus, it is important to understand whether additional cross-talk exists between organ protection pathways and nociceptive signalling pathways when considering available non-opioid analgesics. One example is that transient receptor potential (TRP) channels, including TRP ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1), mediate nociception. Non-opioid analgesics including paracetamol, non-steroidal anti-inflammatory drugs, and COX-2 inhibitors target TRPV1 and TRPA1, which partially contributes to their antinociceptive effects.[2–5]

Activation of TRPA1 and TRPV1 channels are implicated in multiple organ-protecting pathways including those involved in cardiac[6,7] and renal[8] ischaemia–reperfusion injury. The TRPV1 inhibitor capsazepine attenuates the myocardial infarct size reduction afforded by ischaemic preconditioning.[9] TRPV1 knockout mice also show decreased recovery of ischaemia–reperfusion-induced cardiac dysfunction.[9] Further, when TRPA1 or TRPV1 is pharmacologically inhibited, protection by opioids from cardiac reperfusion injury is also abrogated.[6,10]

The involvement of TRP channels in organ-protecting pathways and early evidence demonstrating impaired organ protection through inhibition of TRP channels raise concern regarding the safety of TRP channel antagonists as pain therapeutics. Substantial investment from pharmaceutical companies to develop TRPV1 channel antagonists as pain therapeutics has occurred over the past decade. In 2011, nine different TRPV1 antagonists were in clinical trials, with several completing Phase 2 (Table 1).[11] Although no Phase 3 trials are underway for TRPV1 antagonists, the potential effect of impaired organ protection for these drugs should be entertained if this class of drugs is going to be further pursued.

These concerns might also be important for other novel analgesic targets, such as the nerve growth factor (NGF)/TrkA receptor pathway and the voltage-gated sodium channel 1.7 ($Na_v1.7$). During cardiac ischaemia–reperfusion, NGF is rapidly produced and exogenous NGF administration improves postischaemic dysfunction.[19] NGF also protects PC-12 cells[20] and retinal ganglion cells against ischaemia.[21] Tanezumab (a monoclonal antibody blocking the interaction of NGF with its receptor TrkA) recently received fast track designation by the Food and Drug Administration to treat chronic pain. However, little is known as to whether tanezumab and other drugs targeting the NGF/TrkA pathway might interfere with cellular pathways that provide organ protection. Further, although a role for $Na_V1.7$ in organ ischaemia–reperfusion injury has not been studied, genetic deletion of $Na_v1.7$ can increase enkephalin levels.[22] The increase in enkephalin could protect from organ injury since exogenous enkephalin reduces myocardial infarct size. Therefore, the $Na_v1.7$ pathway will need further investigation and potentially provide an analgesic pathway that does not impair organ protection.

Table 1 TRPV1 channel antagonists tested in clinical trials. An updated table based upon TRPV1 antagonists identified by Moran and colleagues[11] that have been tested in Phase 1 and 2 clinical trials. Some clinical trial results have since been published for these drugs and references are provided. TRPV1, transient receptor potential vanilloid 1; NCT number, National Clinical Trial Number assigned on ClinicalTrials.gov (ClinicalTrials.gov Identifier); IRAS number, the Integrated Research Application System number for the permission and approval for health care research in the UK.

TRPV1 channel antagonist	Clinical phase	Trial registration	Clinical data from trial
ABT-102	1	NCT00854659	Rowbotham and colleagues[12]
AMG-517	2	No registration number	Gavva and colleagues[13]
AZD-1386	2	NCT01019928	Krarup and colleagues[14]
	2	NCT00878501	Miller and colleagues[15]
DWP-05195	1	NCT00969787 and NCT01094834	Lee and colleagues[16]
GRC-6211	2	No registration number	Unpublished
JTS-653	2	No registration number	Unpublished
MK-2295	2	NCT00387140	Unpublished
PHE-377	1	IRAS 88789	Unpublished
SB-705498	1	No registration number	Chizh and colleagues[17]
	1	NCT00731250	Unpublished
	1	NCT01673529	Gibson and colleagues[18]
	2	NCT00281684	Unpublished

Even local infiltration of novel non-opioid analgesics could reduce the ability of remote conditioning to activate cellular protective pathways triggered by nociception.[23] For example, lidocaine infiltration to the abdomen in rodents can block the infarct size sparing effect triggered by nociceptors after a surgical incision.[23] An element of organ protection is also neurally mediated as intrathecal administration of opioids can protect from organ injury as effectively as systemic administration.[24]

Since cross-talk between the organ protection pathways and nociceptive signalling pathways exists, the choice of non-opioid pain medications might be particularly important for surgeries that cause organ ischaemia–reperfusion injury such as cardiac procedures requiring bypass, solid organ transplants,[25,26] and vascular procedures.[27] In the era of precision medicine, perhaps in some subsets of patients the benefits of using opioid-mediated analgesia might outweigh the risks when compared to a multimodal approach to analgesia. Taken together, using non-opioid analgesics or adjuvants for surgery could have unwanted effects in specific patient populations. This should not go unrecognized particularly if novel non-opioid pain therapies become available for use in the future.

Declaration of Interest

None declared.

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Predicting successful supraclavicular brachial plexus block using pulse oximeter perfusion index: is it really an objective outcome?

D. Paul

Armed Forces Medical College, Pune, India

E-mail: drdpaulamc@rediffmail.com.

Editor—In their recent article, Abdelnasser and colleagues[1] studied an objective measure for the assessment of successful peripheral nerve block. I have a few issues regarding the study.

The article did not discuss much about the pulse index (PI) and PI ratio values for the unsuccessful block. These data are of immense importance in view of understanding the changes in PI values when a block fails. It is presumed and subsequently established that a successful block will result in higher PI values and PI ratio values at 10 min from the time of administration of the block. However, we are eager to know the outcome in partial blocks seen with sparing of some nerves to the target area. Here we only see comparative data between the blocked and unblocked arm. Having data for the unsuccessful block would have given more validity to the study.

The article did not discuss the effect of the drugs on blood vessels. The PI value is dependent on pulse amplitude index and is influenced by the amount of blood, not by the concentration of oxygen or the success of the block. Therefore we are actually assessing the effectiveness of block by an indirect method. The authors do not discuss the fact that local anaesthetic in the same vicinity of the major blood vessel (here the subclavian artery) will produce some vasodilation. This change would be reflected in changes of PI value irrespective of the success of the block.

Drugs must be factor in these studies as the use of additives can change the degree of vasodilation. For example, use of