Perioperative Renin-Angiotensin Blockade: To Continue or Discontinue, That Is the Question!

John W. Sear, MS, BSc, MBBS, PhD, FFARCS, FANZCA

Few patients presenting for noncardiac surgery are not receiving 1 or more intercurrent medications. Kaufman et al.[1] examined a cohort of 2590 patients undergoing ambulatory surgery. Eighty-one percent of the patients had been taking at least 1 medication (prescribed drug; over the counter medication; vitamins or minerals; herbals or natural substances) in the week before anesthesia and surgery, and 50% had been taking at least 1 "prescription drug." Further scrutiny shows that 7% of the patients were taking at least 5 prescription drugs, with the highest prevalence in women patients aged over 65 years. Qato et al.[2] suggest that 1 in 25 patients are potentially at risk of a major drug–drug interaction. One such interaction for perioperative patients may be with our anesthetics themselves. The high incidence of comedication has fostered debate about the potential for interactions between general anesthetic agents and preoperative cardiovascular drugs.

One issue far from settled is whether cardiovascular drugs should be maintained throughout the perioperative period. Logic dictates that if an individual needs a medication to control a disease or a pattern of symptoms during daily life (in the absence of the stresses of anesthesia and surgery), then the same drugs are probably needed during the perioperative period. Obvious exceptions include anticoagulants and antihyperglycemic agents. But the maintenance of any drug during the surgical period is subject to the premise that there is low potential for adverse interaction between that drug and the components of general anesthesia. This is why we maintain preoperative β blockers and statins in the perioperative period, because we know that preoperative withdrawal may lead to increased perioperative morbidity and mortality associated with myocardial ischemia and infarction.

Such interactions are certainly possible between anesthesia and cardiovascular drugs. Wolf and McGoldrick[3] reviewed the available literature for such adverse effects and came to the conclusion that β-adrenergic blockers, calcium entry blockers, amiodarone, and α-2 adrenergic agonists can safely be continued up to the time of surgery. They also concluded that angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and diuretics should be discontinued to reduce the incidence of severe hypotension after induction of general anesthesia, and reduce the risks of arrhythmias secondary to hypokalemia and hypomagnesemia.

Are those recommendations, particularly regarding ACE inhibitors and ARBs, appropriate in 2014 given the increasing numbers of patients treated with these drugs in the ambulatory hospital setting? The question seeks equipoise between the risks of hypotension-associated complications if the drugs are continued throughout surgery and the risks of hypertension-associated complications if the drugs are discontinued before surgery.

Surveys and anecdotal reports have revealed that most ACE inhibitors and ARBs are withheld on the day of surgery because of a concern regarding the possible development of refractory hypotension. This is most relevant in patients undergoing surgery where the associated anesthesia may also result in "pharmacologic sympathectomy" (such as during spinal anesthesia), or where there is the risk of significant blood loss. These issues appear to be more relevant in patients receiving ARBs.

When introduced in the 1980s, ACE inhibitors were hailed as "wonder drugs" with 4 positive attributes. First, they provided cardiovascular protection, leading to a reduction in the incidence of ischemic events and their resulting complications. Second, early introduction of ACE inhibition therapy was associated with increased patient survival and improved cardiac function after myocardial infarction. Third, studies showed ACE inhibitors to be effective in the treatment of both heart function and hypertension. Fourth, ACE inhibitors delayed the progression of diabetic nephropathy, But what of their effects in the perioperative period, and is it wise to withhold these drugs?

Physiology and Pharmacology of ACE Inhibitors and ARBs

Renin is a protease enzyme synthesized in the kidney. It catalyzes the conversion of angiotensinogen (a 225 amino-acid prohormone) to angiotensin I. ACE then converts angiotensin I to angiotensin II. The latter protein is a potent vasoconstrictor that acts at angiotensin-1 receptors through a coupling to the phospholipase-C G_q protein /IP_3 transduction pathway. Angiotensin II also facilitates norepinephrine

From the Nuffield Department of Anesthetics. University of Oxford, Oxford, United Kingdom.

Accepted for publication January 30, 2014.

Funding: None.

The author declares no conflicts of interest.

Reprints will not be available from the author.

Address correspondence to John W. Sear, MS, BSc, MBBS, PhD, FFARCS, FANZCA, Nuffield Department of Anesthetics, University of Oxford, Oxford OX3 9DU, United Kingdom. Address e-mail to john.sear@nda.ox.ac.uk.

DOI: 10.1213/ANE.0000000000000204

release and decreases norepinephrine reuptake at sympathetic nerve terminals. Vasoconstriction mediated by the "renin-angiotensin" pathway (RAP) can be blocked at 2 discrete sites, direct inhibition of ACE and angiotensin receptor blockade.

Both ACE inhibitors and ARBs act on the RAP to cause arterial vasodilation by 2 separate mechanisms: limiting the direct effects of angiotensin II on vascular smooth muscle, and by minimizing the ability of angiotensin II to increase sympathetic vascular tone. In addition, their action is accompanied by an increase in parasympathetic tone. As well as these effects on the RAP, they decrease the effect of aldosterone on the distal convoluted tubule of the nephron, thereby promoting salt and water loss.

Inhibition of ACE leads to an inhibition of the breakdown of bradykinin that also contributes to the vasodilator effects of the drugs. However, the increased concentrations of bradykinins may also be responsible for the troublesome unwanted side effects of cough and allergic reactions, as well as others including diarrhea. The ARBs prevent the vasoconstrictor effects of angiotensin II without affecting ACE activity. So, in contrast to ACE inhibitors, ARBs do not affect kinin production. This is why cough is not a prominent side effect of ARBs. They act as selective blockers at angiotensin receptor 1, with no effect on angiotensin receptor 2.

ACE Inhibitors, ARBs, and Anesthesia

The main issues with anesthesia in patients receiving ACE inhibitors or ARBs can be summarized as follows:

- The occurrence of hypotension after induction of anesthesia.
- The occurrence of hypertension after laryngoscopy and intubation, or other noxious stimuli.
- Exaggerated pressor and heart rate responses to noxious stimuli when drugs are withheld preanesthesia and surgery.
- Adverse cardiac outcomes after surgery in patients maintained on these drugs in resistant hypotension, myocardial infarction, and cardiac death.

In the hypertensive patient, there are few studies examining the effects of maintaining ACE inhibitors and ARBs on the renin-angiotensin system (RAS), comparing the responses to induction of anesthesia, and to noxious stimuli of patients on ACE inhibitors and ARBs with the responses in patients maintained on other antihypertensive therapies. Colson et al, Coriat et al, Pigott et al, Bertrand et al, Comfere et al, and Weisenberg et al.[4–9] reported a greater incidence of hypotensive episodes after induction of anesthesia in patients in whom therapy was continued up to the day of surgery. In a meta-analysis of all available data (encompassing 5 studies of 434 patients), Rosenman et al.[10] showed that continuing drugs up to the morning of surgery was more likely to lead to hypotension at or following induction of anesthesia with a need for vasopressor to restore the blood pressure to normal levels.

However, in a small study comparing the cardiovascular responses to induction of anesthesia, and to laryngoscopy and intubation in mild to moderate hypertensive patients, we studied 5 groups of patients receiving one or other of the following monotherapies: ACE inhibitors; β-adrenoceptor blockers; calcium channel blockers; diuretics; and diagnosed but untreated hypertension.[11] Drugs were continued up to and including the morning of surgery. There were no significant differences in the responses of blood pressure and heart rate after induction of anesthesia with thiopental and fentanyl. However, there was a reduced heart rate response in the β-blocked group of patients to laryngoscopy and intubation. The responses in terms of cardiac output and systemic vascular resistance were similar in the 5 groups. Although the anesthetic technique used in that study may have been superseded and no longer remains the one of choice, there is no evidence that interactions among the 4 groups of drugs and propofol will be significantly different (in the presence of accompanying dosages of 100 ug fentanyl). These findings have been mirrored in the findings of Schulte et al.[12] using a total IV anesthesia technique for minor surgery and noting no hemodynamic differences between patients receiving ACE inhibitors and those not.

Other outcome data in patients on ACE inhibitors or ARBs can be divided into 2 areas: the effects of RAS inhibition on auto-regulation; and the effect of drug therapies on morbidity and mortality. There is evidence from Licker et al.[13] that RAS inhibition by chronic ACE inhibitor therapy does not influence cardiac autonomic regulation. Drug therapy had no effect on the heart rate variability or on baroreflex sensitivity either during the awake period preoperatively or during steady-state anesthesia. The occurrence of anesthetic-induced hypotensive episodes after induction with midazolam-fentanyl could be mainly attributed to a decrease in the normal α-adrenergic vasoconstrictor response. Indeed, Prys-Roberts,[14] in correspondence following the study by Bertrand et al.,[7] suggested that if anesthesiologists plan to maintain ACE inhibition or angiotensin receptor blockade, they should consider prophylactic use of glycopyrrolate or similar anticholinergic drugs to minimize bradycardia and hypotension.

Behnia et al.[15] suggest that the hemodynamic variation seen during anesthesia is mainly because of the effects of anesthesia on the sympathetic nervous system. If the patient has undergone a long period of preoperative fasting, or is volume depleted, or is receiving an anesthetic-induced extended sympathetic blockade, then there is a high probability of marked hypotension, which will be exaggerated by the coadministration of diuretics and/or RAS inhibitors.

The interaction of ACE inhibitors or ARBs and anesthesia on long-term outcomes has recently been evaluated by 3 large cohort studies.[16–18] Remarkably, 3 studies found the 3 possible conclusions. Railton et al.[16] found that maintenance of RAS blockade was associated with increased mortality in vascular surgical patients (odds ratio 5.0; 01.4–27.0). Toppin et al.[17] reported that maintenance of RAS blockade was associated with decreased mortality in a case-control study of 14,400 patients undergoing noncardiac surgery (odds ratio 0.59; 0.44–0.71). Turan et al.[18] found no difference in either 30-day mortality or respiratory complications when the drugs have been withheld preoperatively. Is it any wonder that clinicians remain confused?

Often neglected in this discussion is consideration of the preoperative risks to the patients when antihypertensive drugs are discontinued on the day of surgery. In a randomized controlled trial reported in this issue of the journal, Twersky et al.[19] examined the hemodynamic consequences

of continuation or discontinuation of ACE inhibitors and ARBs in 506 patients undergoing ambulatory or same day surgery. They found that discontinuation of ACE inhibitors and ARBs was neither associated with an increased prevalence of preoperative hypertension nor postoperative hypertension, prolonged hospital stay, or adverse clinical events.

How should anesthesiologists handle these patients? The case for discontinuing therapies does not seem to be overwhelming. Coupled with the data from the study of Toppin et al.,[17] the anesthesiologist might consider maintaining the drug therapies. The lack of any difference in the prevalence of preoperative and postoperative hypertension in the study by Twersky et al.[19] may reflect a longer efficacy of drug therapy than previously imagined. However, the authors include neither data about the effects of continuation or discontinuation on the hemodynamic response to induction of anesthesia, nor on the response to noxious stimuli, nor on whether standardized anesthesia and analgesia protocols were adopted in all patients (which might influence the prevalence of any adverse effects).

Whichever policy is adopted in the management of these patients, the anesthesiologist should be aware of the potential adverse effects of the interactions between anesthesia and drug therapy. Fortunately, nobody is more knowledgeable, or better prepared, to treat acute hemodynamic compromise than we are.

DISCLOSURES

Name: John W. Sear, MS, BSc, MBBS, PhD, FFARCS, FANZCA.
Contribution: This author wrote the manuscript.
Attestation: This author approved the final manuscript.
This manuscript was handled by: Steven L. Shafer, MD.

REFERENCES

1. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002;287:337–44
2. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008;300:2867–78
3. Wolf A, McGoldrick KE. Cardiovascular pharmacotherapeutic considerations in patients undergoing anesthesia. Cardiol Rev 2011;19:12–6
4. Colson P, Saussine M, Séguin JR, Cuchet D, Chaptal PA, Roquefeuil B. Hemodynamic effects of anesthesia in patients chronically treated with angiotensin-converting enzyme inhibitors. Anesth Analg 1992;74:805–8
5. Coriat P, Richer C, Douraki T, Gomez C, Hendricks K, Giudicelli JF, Viars P. Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. Anesthesiology 1994;81:299–307
6. Pigott DW, Nagle C, Allman K, Westaby S, Evans RD. Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements. Br J Anaesth 1999;83:715–20
7. Bertrand M, Godet G, Meersschaert K, Brun L, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued before surgery? Anesth Analg 2001;92:26–30
8. Comfere T, Sprung J, Kumar MM, Draper M, Wilson DP, Williams BA, Danielson DR, Liedl L, Warner DO. Angiotensin system inhibitors in a general surgical population. Anesth Analg 2005;100:636–44
9. Weisenberg M, Sessler DI, Tavdi M, Gleb M, Ezri T, Dalton JE, Protianov M, Zimlichmann R. Dose-dependent hemodynamic effects of propofol induction following brotizolam premedication in hypertensive patients taking angiotensin-converting enzyme inhibitors. J Clin Anesth 2010;22:190–5
10. Rosenman DJ, McDonald FS, Ebbert JO, Erwin PJ, LaBella M, Montori VM. Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period. J Hosp Med 2008;3:319–25
11. Sear JW, Jewkes C, Tellez JC, Foëx P. Does the choice of antihypertensive therapy influence haemodynamic responses to induction, laryngoscopy and intubation? Br J Anesth 1994;73:303–8
12. Schulte E, Ziegler D, Philippi-Höhne C, Kaczmarczyk G, Boemke W. Angiotensin-converting enzyme inhibition and blood pressure response during total intravenous anaesthesia for minor surgery. Acta Anesthesiol Scand 2011;55:435–43
13. Licker M, Schweizer A, Höhn L, Farinelli C, Morel DR. Cardiovascular responses to anesthetic induction in patients chronically treated with angiotensin-converting enzyme inhibitors. Can J Anesth 2000;47:433–40
14. Prys-Roberts C. Withdrawal of antihypertensive drugs before anesthesia. Anesth Analg 2002;94:767–8
15. Behnia R, Molteni A, Igić R. Angiotensin-converting enzyme inhibitors: mechanisms of action and implications in anesthesia practice. Curr Pharm Des 2003;9:763–76
16. Railton CJ, Wolpin J, Lam-McCulloch J, Belo SE. Renin-angiotensin blockade is associated with increased mortality after vascular surgery. Can J Anesth 2010;57:736–44
17. Toppin J, Naughton F, Wijeysundera D, Tait G, Beattie S. ACE inhibitors reduce 30 day mortality after non-cardiac surgery. Abstracts SCA 2011;SCA 64
18. Turan A, You J, Shiba A, Kurz A, Saager L, Sessler DI. Angiotensin converting enzyme inhibitors are not associated with respiratory complications or mortality after noncardiac surgery. Anesth Analg 2012;114:552–60
19. Twersky R, Goel V, Narayan P, Weedon J. Risk of hypertension after preoperative discontinuation of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists in ambulatory and same day admission patients. Anesth Analg 2014