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Perioperative management of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

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Abstract

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) reduce cardiac remodelling, fibrosis, and inflammation. High-risk surgical patients requiring non-cardiac surgery are frequently prescribed ACEIs or ARBs as first-line therapy for hypertension and other conditions, including heart failure, myocardial infarction (MI) and stroke, diabetes mellitus leading to diabetic nephropathy, etc. However, the continuation of ACEIs or ARBs in the perioperative period has been associated with an increased risk of intraoperative hypotension. The data on the perioperative management of these medications are limited. Consider, a 73-years-old woman with hypertension and type 2 diabetes having bilateral salpingo-oophorectomy for ovarian cancer. Her medications included ramipril, amlodipine, and oral hypoglycaemic agents. The ramipril was continued perioperatively, and besides transient but severe hypotension at induction of anaesthesia, the patient's course was unremarkable. The present case-based review discusses the current controversies surrounding the perioperative management of ACEIs and ARBs.

Introduction

Angiotensin II is a crucial component of the pathogenesis of hypertension. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) reduce cardiac remodeling, fibrosis, and inflammation [1]. High-risk surgical patients requiring non-cardiac surgery are frequently prescribed ACEIs or ARBs as first-line therapy for hypertension and other conditions, including Heart Failure, myocardial infarction (MI) and stroke, diabetes mellitus leading to diabetic nephropathy, etc [2].

Clinical scenario

A 73-years-old ex-smoker with diabetes, hypertension and stage 2 chronic kidney disease was scheduled for bilateral salpingo-oophorectomy for ovarian cancer. On review in the pre-anaesthetic clinic, although her blood pressure was controlled with ramipril and amlodipine, the HbA1c was elevated (8.1%) despite oral hypoglycaemic agents. At the clinic, it was decided that the patient should not stop her antihypertensive medication prior to surgery. However, at induction of anaesthesia, the patient's blood pressure fell precipitously. Intravenous fluids and vasopressors were required to maintain the mean arterial blood pressure over 65 mmHg intraoperatively. The patient's perioperative course was otherwise unremarkable. In this context, it is important to consider the controversies surrounding the perioperative management of drugs acting on the Renin-Angiotensin System (RAS).

Discussion

The latest National Institute for Health and Care Excellence (NICE) guidelines on hypertension recommend the use of ACEIs or ARBs as first-line therapy for hypertension in patients with type 2 diabetes and patients of non-Afro-Caribbean origin aged less than 55 years [3]. The Eighth Joint National Commission (JNC8) also recommends the use of ACEI or ARBs for the initial treatment of hypertension [4].

In the last century, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial demonstrated the efficacy and safety of ACEIs in the treatment of heart failure [5]. The findings of CONSENSUS were strongly supported by the Studies of Left Ventricular Dysfunction (SOLVD) trial [6]. Both trials reported a significant decrease in mortality in patients on enalapril [5,6]. In the Valsartan Heart Failure Trial (Val-HeFT), valsartan was shown to significantly reduce the mortality and morbidity of patients with heart failure [7].

In the Preventing Strokes by Lowering Blood Pressure in Patients with Cerebral Ischemia (PROGRESS) trial, 6105 individuals with a history of stroke or transient ischemic attack were randomly allocated to receive perindopril (with indapamide) or placebo [8]. Over a 4-year follow-up period, the PROGRESS trial investigators reported a 28% relative risk (RR) reduction in patients receiving perindopril.

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The heart outcomes prevention evaluation (HOPE) study evaluated the impact of ramipril in high-risk patients without signs of heart failure but who were older than 55 years with diabetes or vascular disease and another cardiovascular risk factor [9]. The RR of myocardial infarction, cardiac arrest, heart failure, diabetes complications, and overall cardiovascular death were substantially reduced in the treatment arm on five-year follow-up [9].

Vast amounts of high-quality data support the long-term benefits of treatment with ACEIs and ARBs [1-9]. However, the evidence on which to base the management of ACEIs and ARBs in the perioperative setting is limited. Regardless it is important to consider whether they should be stopped or continued throughout?

The 2014 European Society of Cardiology / European Society of Anaesthesiology (ESC/ESA) guidelines recommended that ACEIs or ARBs be continued carefully in the perioperative period in patients with heart failure or LV dysfunction presenting for non-cardiac surgery [10]. When prescribed for hypertension, temporary cessation is recommended [10].

On the other hand, the American College of Cardiology / American Heart Association (ACC/AHA) guidelines of the same year imply that it is appropriate to continue taking ACEIs or ARBs throughout the perioperative period [9]. The ACC/AHA guidelines also recommend that, if stopped, ACEIs or ARBs should be reintroduced as soon as clinically practicable postoperatively [11].

These conflicting guidelines make perioperative management of ACEIs and ARBs difficult for many clinicians. The Vascular events in non-cardiac Surgery Patients Cohort Evaluation (VISION) trial is a comprehensive prospective cohort study examining the perioperative usage of ACEIs and ARBs in non-cardiac surgery [12]. There were no significant differences in perioperative morbidity or mortality between those patients who continued ACEIs or ARBs in comparison to those who discontinued these medications [12].

The ongoing STOP-or-NOT trial is evaluating the impact of continuation or discontinuation of ACEIs and ARBs on perioperative complications in patients undergoing major non-cardiac surgery [13]. It is a multicenter, open-label randomised controlled trial [13]. In the control arm, ACEIs/ARBs will be stopped 48 hours before surgery. The treatment group will continue these medications throughout the perioperative period. It is hoped that this trial will provide a definitive answer to the question of how best to manage ACEIs/ARBs perioperatively. Regardless, in the interim, it is important to pragmatically consider what should be done with these medications.

In the absence of universal guidelines supporting the perioperative continuation of ACEIs/ARBs; several local policies recommend that these drugs be withheld on the morning of surgery. This advice intends to prevent excessively low blood pressures and organ hypoperfusion in the perioperative period. However, the risk-benefit ratio of discontinuing these medications should be carefully considered. Patients with resistant hypertension or heart failure should probably continue taking ACEIs/ARBs throughout the perioperative phase. If hypovolaemia is avoided and drops in blood pressure are treated promptly and adequately with fluid boluses and vasoconstrictors, the potential advantages of this strategy may exceed the dangers [14]. Some data suggest that perioperative continuation of RAS antagonists may offer renoprotection, a decreased risk of perioperative AF, and neuroprotection after cerebrovascular operations [15].

Novel agents which combine an ARB with a neprilysin inhibitor (Angiotensin Receptor Neprilysin Inhibitors (ARNI)) have been shown to improve outcomes in heart failure [16]. Sacubitril/valsartan is the first ARNI to be approved by FDA; its perioperative use, however, is yet to be examined.

It is clear that ACEIs, ARBs, and ARNI are very beneficial in the treatment of a range of cardiometabolic conditions [2]. Delaying the reintroduction of these drugs postoperatively may significantly increase mortality [17].

Conclusion

Whilst the ongoing trials are likely to answer some questions, the scope for research on the perioperative use of ACEIs, ARBs, and ARNI remains vast. Yet, until more specific and definitive studies are completed, robust, didactic, evidence-based guidelines on perioperative management of ACEIs and ARBs remain elusive. Every anaesthetist must carefully weigh the risks and benefits taking decisions on a case-by-case basis to avoid harm whilst maximizing the value of ACEIs/ARBs throughout the perioperative period [17].

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