

No consensus on withholding angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before spinal anaesthesia

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ABSTRACT

INTRODUCTION: Danish (including Greenland and the Faroe Islands) and international guidelines were reviewed to determine to which extent they recommend the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) before spinal anaesthesia.

MATERIAL AND METHODS: A total of 50 Danish departments of anaesthesia and 30 societies of anaesthesiology were invited by e-mail to detail their guidelines on pre-anaesthesia ACE inhibitor and ARB use and the number of registered deaths due to hypotension. PubMed was searched for existing guidelines.

RESULTS: Seven of 31 responding departments in Denmark had issued guidelines. None of 11 responding societies except the French had issued guidelines. The French society recommended discontinuation of ACE inhibitors and ARBs for hypotension > 12 hours before surgery, but no discontinuation in case of heart failure. None of the societies reported deaths.

CONCLUSION: A minority of the responding Danish departments of anaesthesia and the French Society of Anaesthesiologists have issued guidelines on the use of ACE inhibitors and ARB, but extant literature is scant and equivocal, and no randomized trials have studied either the indications for or the adverse outcome of ACE inhibitors and ARB treatment.

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Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are drugs used for controlling arterial hypertension (HT), congestive heart failure (CHF) and diabetic nephropathy, among others. These drugs were developed several decades ago, but clear guidelines or recommendations on their use do not exist although several studies have reported severe, even fatal, side effects like hypotension when they are used in surgery patients before anaesthesia [1-5]. A pertinent question is therefore if the use of ACE inhibitors and ARBs should be discontinued in patients in general, and whether guidelines and recommendations on the subject should make a distinction between general anaesthesia (GA) and neuraxial anaesthesia as the haemo-

dynamic effects are related to the spinal level of the anaesthesia and the attenuation of the efferent sympathetic pathway drive.

The aim of the present paper is to determine to which extent national Danish guidelines, international guidelines and the current literature recommends discontinuation of ACE inhibitor and ARB administration before spinal anaesthesia (SA) in patients undergoing elective surgery. The Danish Society of Anaesthesiology and Intensive Care Medicine, for example, has issued no guidelines or recommendations in this respect.

MATERIAL AND METHODS

During the first six months of 2012, 50 Danish (including Greenland and the Faroe Islands) departments of anaesthesia were invited by e-mail to answer the following questions: Do departmental guidelines or recommendations specify ACE inhibitor and ARB use on the day of surgery involving SA? Affirmative answers prompted sub-questions: What are your guidelines? Do you distinguish between ACE inhibitors and ARBs or are the two drugs considered equal in this context? Do you distinguish between ACE inhibitor and ARB doses? Do you distinguish between different patient categories? What are the consequences if a patient ignores advice on pre-surgery ACE inhibitor and ARB use? Do you routinely optimize patients who have ignored such advice? All departments were also asked whether severe hypotension or deaths had occurred in connection with ACE inhibitor and ARB use during SA over the past decade.

Thirty international societies of anaesthesiology were invited by e-mail to answer the question: Do you have guidelines or recommendations on the use of ACE inhibitors and/or ARBs on the morning of SA? Affirmative answers prompted sub-questions: What are the guidelines or recommendations? Have cases of cardiovascular collapse due to ACE inhibitor and/or ARB use on the morning of SA been communicated to you? Have you conducted studies on this subject?

A literature search was performed in PubMed using the keywords "spinal anaesthesia AND angiotensin converting enzyme inhibitor", "spinal anaesthesia AND ace", "spinal anaesthesia AND angiotensin receptor blockers",

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“spinal anaesthesia AND arb” and “spinal anaesthesia AND hypotension”. The following filters were used: human material; both sexes; adults; Danish, English, French & German language & publication dates from 1970. Relevant MeSH-terms were applied. The references of these papers were searched for further articles.

Trial registration: not relevant.

RESULTS

National approach

Among 31 departments, two did not use SA, 22 had no guidelines or recommendations and none had encountered cases of severe, treatment-resistant hypotension or death.

One department reported having many weak patients (often with CHF) undergoing vascular surgery. Anaesthesiologists were not requested to pause ACE inhibitors and ARBs, but patients were always assessed. Another department reported using low-dose bupivacaine (5-8 mg) and rare cases of cardiovascular side-effects.

Two departments reported consensus, but had no guidelines on continuation of ACE inhibitors and ARBs in patients with CHF or left-ventricular failure, but not in patients with HT. Finally, two departments reported that discontinuation was subject to debate.

Among the remaining seven departments with guidelines, five recommended pausing. Two recommended pausing in all patients except those with CHF. If patients had taken the drugs despite advice to the contrary, three departments would continue as planned, whereas four would continue only after assessment of the patient's condition and the scheduled surgery. Optimization with fluid before SA was standard practice at four departments; symptomatic fluid and vasopressor treatment was provided by all departments. None reported any deaths. A few departments mentioned that “the expected hypotension” after SA was corrected with fluids and vasopressors, but only two reported a single case of severe, treatment-resistant hypotension. All departments equated ACE inhibitors with ARBs.

International approach

A response was obtained from eleven societies: Australia, France, Great Britain & Ireland, Italy, Norway, South Africa, Spain, Sweden, Switzerland, United States and the World Federation of Societies of Anaesthesiologists (WFSA). According to expert opinion and using a Delphi method, only La Société Française d'Anesthésie et de Réanimation (SFAR) had guidelines or recommendations [6]. The SFAR recommends drug pausing > 12 hours before surgery for HT, but continuance in treatment for cardiac failure. It also recommends that the risk of hypotension and surgery be considered in each case. No society had been informed of or had registered cases of death. Furthermore, only the WFSA could refer to a study of ACE inhibitors and ARBs and SA [7].

The American Society of Anesthesiologists (ASA) has no guidelines or recommendations according to the Chair of the ASA Committee on Regional Anesthesia, but in his capacity as Clinical Practice Chair of the Mayo Clinic's Department of Anesthesiology, he reported that all patients are requested to hold their dose of ACE inhibitors and ARBs on the morning of surgery, regardless of whether or not they will be receiving SA. Swedish national guidelines do not exist, but the President of the Swedish Society of Anaesthesiology & Intensive Care at Sahlgrenska University Hospital reported that they strongly advise pausing from the day before surgery. Despite the absence of guidelines, the spokesman of La Société Suisse d'Anesthésiologie et de Réanimation reported that he recommended a minimum interval of eight hours between ingestion of ACE inhibitors and ARBs and SA. He emphasized the importance of distinguishing between lipophilic hyperbaric (e.g. bupivacaine hyperbar) and hydrophilic isobaric (e.g. prilocain isobar) local anaesthetics. The latter tend to spread cephalad long after initiation due to delayed elimination from the spinal fluid which depresses sympathetic innervation even at low concentrations. The replies from the WFSA and the Australian and New Zealand Colleges of Anaesthetists highlighted as important factors the patient's condition, the practitioner's experience, how SA is administered and the surgery performed.

LITERATURE

The present literature on ACE inhibitors and ARBs in connection with anaesthesia has focused, e.g., on haemodynamic instability in relation to GA. In a randomized controlled trial (RTC) on hypertensive patients (n = 56) receiving ACE inhibitors pre-surgery [8], ACE inhibitor therapy was discontinued on the morning of surgery in a sub-group of patients with HT scheduled for vascular surgery in GA. The results indicated an increase in the probability of hypotension at induction in the group where ACE inhibitor treatment was not paused



ABBREVIATIONS

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blockers
ASA = American Society of Anesthesiologists
CHF = congestive heart failure
GA = general anaesthesia
HT = hypertension
RCT = randomised controlled trial
SA = spinal anaesthesia
SFAR = Société Française d'Anesthésie et de Réanimation
WFSA = World Federation of Societies of Anaesthesiologists



Should angiotensin-converting enzyme inhibitors & angiotensin receptor blockers be paused prior to this?



Are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to be withheld before spinal anaesthesia?

($p < 0.05$). Comfere et al [9] retrospectively studied patients with HT patients receiving ACE inhibitors or ARBs ($n = 267$) undergoing elective non-cardiac surgery in GA.

Discontinuation a minimum of ten hours before anaesthesia was associated with a reduced risk of immediate post-induction hypotension ($p = 0.04$). Sixty minutes after induction, hypotension was similar in the groups ($p = 0.97$). In a prospective randomised study of haemodynamics during GA in patients ($n = 37$) treated with ARBs because of HT [10], one group discontinued ARBs one day before surgery and the other group received ARBs one hour before surgery. The latter group had a decrease in systolic arterial pressure associated with more frequent episodes of hypotension ($p < 0.05$). The study concluded that discontinuation of ARBs may be justified.

A randomised, single-blinded, controlled study ($n = 334$) of the impact of discontinuing ACE inhibitors and ARBs in the pre-operative period in ambulatory same-day patients hypothesized that discontinuation might predispose to pre-operative HT [11]. However, discontinuation > 10 hours pre-operatively neither increased the incidence of pre- or peri-operative HT, nor meant that surgery had to be cancelled. Tohmo et al [12, 13] questioned the practice of discontinuing ACE inhibitor use before anaesthesia, arguing that if the patients were properly hydrated, there would be no more cases of hypotension than seen with other vasodilators, diuretics or cardiodepressant drugs. A review by Smith et al [14] acknowledged the likelihood of intra-operative hypotension if ACE inhibitor and ARB treatment is continued, but they argued that it may be countered by simple treatment (e.g. with fluids) and is associated with no apparent adverse outcomes. They suggested that patients be instructed to take all cardiac medications as normal and recommended that ACE inhibitors and ARBs should not be given to patients who have forgotten to take these drugs.

Only a single RCT has explored the use of ACE inhibitors and ARBs in neuraxial anaesthesia. The study ($n = 42$) investigated if long-term treatment with ACE inhibitors impairs the haemodynamic regulation during the early phase of SA [7] and reported no additional ACE inhibitor-induced depression of blood pressure. The question whether or not the patients should take ACE inhibitors and ARBs before SA was not addressed. Hopf et al [15] studied ($n = 10$) how thoracic epidural anaesthesia suppresses renin release in response to arterial hypotension and hence interferes with the sympathetic system, but the use of ACE inhibitors and ARBs was not examined.

Auron et al [16] published a review of the use of ACE inhibitors and ARBs in the peri-operative setting; a short section on neuraxial anaesthesia concluded that although evidence is limited and contradictory, it appears safe to discontinue ACE inhibitor and ARB treatment before spinal anaesthesia until further RCTs have been performed, i.e. to withhold the drugs for one half-life before induction of anaesthesia. Adequate intravenous volume and haemodynamic monitoring was recommended if the drugs could not be withheld before induction of anaesthesia. In a review by Behnia et al [17], no conclusion was reached as to continuation or discontinuation before SA. The Norwegian Anaesthesiological Society quoted Ræder et al [18] who recommend ACE inhibitor and ARB pausing from the night before and on the day of surgery both in general and regional anaesthesia, including SA.

DISCUSSION

With apparently no deaths during the past ten years due to ACE inhibitor and ARB use on the day of surgery involving SA, the subject seems to represent no major problem at Danish departments of anaesthesiology, i.e. if the endpoint is death due to cardiovascular collapse and the respondents' answers are generalizable. Danish approaches vary and simple counter measures like fluid and vasopressor treatment of symptoms seem to suffice.

TABLE 1

Variables to take into consideration in relation to spinal anaesthesia.

Spinal level of anaesthesia
Choice of anaesthetics
Baricity (isobaric vs. hyperbaric)
Lipophilicity of anaesthetics
Hydrophilicity of anaesthetics
Volume of anaesthetics (e.g. ml)
Dosage of anaesthetics (e.g. mg)
Additives (e.g. clonidine and opioids)
Patient's condition (e.g. dehydration)
Patient's co-morbidities (e.g. ischaemic heart disease)
Surgical procedure (e.g. blood loss)
Properties of the angiotensin-converting enzyme inhibitors & angiotensin receptor blockers in use (e.g. half-life)
Diuretics added to the angiotensin-converting enzyme inhibitor and angiotensin receptor blocker pills
Practitioner's experience
Technical aspects (e.g. spinal catheter)

Only the SFAR has official guidelines, but there seems to be a tendency towards withholding ACE inhibitors and ARBs on the day of surgery, or even the day before, due to the risk of haemodynamic instability. No society or comments favoured using ACE inhibitors and ARBs on the day of surgery.

The literature is scant and the issue of ACE inhibitor and ARB use before SA has not been explored in RCTs. The present paper focuses on the risk of cardiovascular instability with hypotension in the peri-operative setting, but future studies should include more potential adverse outcomes (e.g. myocardial infarction). As appears from **Table 1**, many variables need to be considered. Patients are often fasting for many hours before anaesthesia, and the question is therefore whether optimised fluid therapy would end the discussion. Present studies have focused on ACE inhibitors and ARBs in relation to GA and have shown a tendency to increased hypotension [8-10].

In the absence of scientific consensus, specifying guidelines is like stirring up a hornets' nest. HT and CHF are the two main indications for the use of ACE inhibitors and ARBs. Concerning HT, most papers favour discontinuing treatment on the day of SA or a half-life 8/12 hours before surgery. The latter is in accordance with SFAR guidelines. If the patient has ignored advice to pause drug usage, hypotension will generally respond to fluid and vasopressor treatment, i.e. treatment should continue as planned. But cases resisting such treatment have been reported [4, 19]. The question of continuance or discontinuance of ACE inhibitor and ARB treatment is more controversial in patients with CHF who may suffer from co-morbidities and be weak. To avoid drug holidays, the SFAR recommends not to withhold ACE inhibit-

ors and ARBs and so do Tohmo et al [12]. But the other reviews and studies mentioned recommend withholding treatment. Involving a cardiologist for an individual assessment seems prudent in patients with CHF. One Danish department had many weak patients (often with CHF) undergoing vascular surgery who were informed not to pause their medication before surgery, but each individual patient was always assessed. The essence is that ACE inhibitors and ARBs may be given, but this should always be preceded by individual assessment. Discontinuation may be appropriate for other indications than CHF, but we clearly need more RCTs in this field. Patient categories with co-morbidities and polypharmacy represent a challenge that should be addressed in future studies.

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CONFLICTS OF INTEREST: none

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