Official Title: A Dose Finding Trial for Angiotensin II in Hypertensive Adults on Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with Anesthesia-Mediated Hypotension

NCT03733145

IRB Approval Date: 10/20/2020

Study Title: A Dose Finding Trial for Angiotensin II in Hypertensive Adults on Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with Anesthesia-Mediated Hypotension

Principal Investigator, Co-investigator(s): Rohesh J. Fernando, MD, FASE; Wes Templeton, MD; Roger Royster, MD; Ashley Talbott, MD; Sarah Kittner, MD; Ben Morris, MD; Chandrika Garner, MD; Darryl Henshaw, MD; Leanne Groban, MD; Carlos Ferrario, MD; Ashish Khanna, MD;

Sponsor or funding source: This study will be primarily funded by the department of anesthesia and will be partially funded by the National Institutes of Health. In addition, La Jolla Pharmaceutical Company will be supporting the study in the amount of $19,926.

Background, Rationale and Context

Hypotension in adult patients undergoing general anesthesia is common. Many of the body's normal mechanisms to maintain adequate blood pressure in the non-anesthetized state are significantly altered by anesthetic agents, which may lead to hypotension. In addition, anesthetic agents themselves can contribute to hypotension by a variety of mechanisms, including vasodilation. The resultant hypotension can lead to hypoperfusion of vital organs, organ damage, and states of increased metabolic duress. This may be worse in patients with underlying essential hypertension and can even be further exacerbated in patients taking ACE inhibitors and ARBs.[1] In response to this it has become standard of care to attempt to maintain blood pressure levels within 20% of baseline in most patients under anesthesia.[2] Maintaining the baseline blood pressure is important as patients may have pathology such as coronary artery disease, carotid stenosis, and renal artery stenosis, and hypotension may compromise the perfusion of these organs.

At this time there are a number of vasopressor agents which are commonly used to increase blood pressure in anesthetized patients undergoing surgery. These agents work either directly or indirectly through adrenergic receptors present in vascular smooth muscle and are in many ways non-specific vasoconstrictive agents. Some also affect contractility of the heart and can impact blood pressure through this mechanism as well. Angiotensin II (Ang II) is an endogenous peptide that is part of the renin-angiotensin-aldosterone system (RAAS). The RAAS plays an integral role in maintaining and regulating blood pressure under normal physiologic conditions. In a randomized controlled trial, the ATHOS-3 investigators found that Ang II was effective in raising blood pressure in patients with refractory vasodilatory shock.[3]

As stated previously, vasodilation also plays a key role in hypotension due to general anesthesia. Therefore, the intravenous (IV) administration of Ang II may also be an effective treatment of hypotension in this patient population. However, the dose or infusion rate that would be most effective at treating hypotension in patients under general anesthesia is currently unknown. Additionally, it is unknown if patients with essential hypertension taking ACE inhibitors or ARBs will respond differently than patients not taking these agents.

In addition to measuring levels of Ang II (classic RAAS system), we also wish to study other components of RAAS. For example, angiotensin 1-7 provides counter regulation to the classic RAAS and increases in response to ACE inhibitors and ARBs.[4] Bradykinin can also be responsible for hypotension and is potentiated by angiotensin 1-7. RAAS sampling could therefore allow a more comprehensive understanding of hypotension in our study population and provide a framework to better interpret results. RAAS testing can be done using liquid chromatography / mass spectrometry (LC/MS) or radioimmunoassay (RIA).

Objectives

The primary objective of this study is to determine the infusion rate of Ang II that is necessary to return systolic blood pressure (SBP) to within 5% of baseline or greater in patients with essential hypertension taking ACE inhibitors, ARBs, or different classes of antihypertensive agents for greater than two months and further to determine the plasma levels of different RAAS components (as measured by the Attoquant system) in patients preoperatively, following induction, at a steady state infusion level of Ang II, and 30 minutes after surgical incision. In addition, a secondary objective is to determine how the levels of various RAAS components in the blood compare based on the method of analysis (liquid chromatography versus radioimmunoassay).

Methods and Measures

Design

Patients scheduled for general surgery who are evaluated in our preoperative assessment clinic (PAC) will be recruited for participation. Recruitment and consent for participation in the study will be performed prior to day of surgery via telephone screen or in person at the PAC. If patient is consented via telephone screen and agrees to participate, a consent form will be electronically mailed, or physically mailed to the patient. Patient will be asked to sign consent and return electronically or by physical mail. Patient will also sign consent in person on day of, prior to surgery. Once initial consent is received, (Giapreza) will be prepared and ready for use during surgery. Women of childbearing age will be asked about level of sexual activity and use of birth control. Given that the safety of Ang II has not been demonstrated in pregnant patients, the only women of childbearing age who will be considered for recruitment are those that (1) are not sexually active; or (2) are sexually active and use an acceptable method of birth control; or (3) are surgically sterile; or (4) are at least 2 years postmenopausal; or (5) have a monogamous partner who is surgically sterile; or (6) are practicing double barrier contraception. Once recruited, we will verify on the day of surgery that the patient is still agreeable to participate in the study. Women of childbearing age will be asked to undergo a pregnancy test on the day of surgery and provide a negative result. The determination of whether the patient takes their anti-hypertensive on the day of surgery will be determined by the PAC's normal practice and will be unaltered by this study. Our goal would be to enroll and obtain data on 15 patients for each group: (Arm 1) ACE group, (Arm 2) ARB group, and (Arm 3) patients on any other class of antihypertensive agent for greater than two months. There will also be a fourth comparison group (Arm 4) consisting of up to the first 15 enrolled patients whose SBP does not drop below the 80% baseline threshold after intubation. It would be our intent to continue enrolling patients until a sample size of 15 patients for each of the 3 groups (Arms 1,2,3) have completed the protocol and received the trial medication. Once each of the three experimental arms of the study (Arms 1,2,3) have 15 patients, enrollment in the fourth comparison group (Arm 4) will cease regardless of whether or not it has met the 15 patient goal. Based on an estimated incidence of hypotension of 40-60% following induction of anesthesia, we expect to have to consent approximately 90 patients. This is to account for patients who do not meet study criteria, thereby reaching our goal of 45 experimental patients and the tentative 15 patient comparison group.[1]

There will be a total of 5 blood samples taken at three time points throughout the duration of the study. Patients will have an IV line placed in the holding area prior to surgery. At this time, we will draw the first two 10cc blood samples (one for LC/MS analysis, one for RIA analysis) for study purposes while the patient is in the preoperational holding room. The RIA labs will be processed at Wake Forest Baptist Medical Center and is sponsored by a grant from the NHLBI of the NIH. , and the LC/MS labs will be analyzed through an external contracted laboratory to gain information for RAAS component testing. An initial set of vital signs including heart rate (HR),

non-invasive blood pressure (BP), and oxygen saturation (SpO2) will be checked in the holding room. We will also record all medications taken on the day of surgery. Once in the operating room and following placement of vital sign monitors, another non-invasive BP will be checked prior to anesthetic induction. This reading will be used as the baseline systolic blood pressure (SBP). Sequential Compression Devices (SCD) will be used for venous thromboembolism (VTE) prophylaxis during surgery and these will be applied prior to induction of general anesthesia. General anesthesia will then be induced with 1.5 mg/kg of propofol followed by 0.8 mg/kg rocuronium and the patient will be intubated. If the dose of propofol is inadequate to achieve loss of consciousness, additional propofol may be given at the discretion of the attending anesthesiologist. In addition, a rapid sequence induction and intubation may also be allowed if clinically indicated for the safety of the patient as determined by the attending anesthesiologist. Anesthesia will be maintained with isoflurane in fresh gas such as oxygen and/or air. No vasopressors will be administered at induction or during intubation unless the SBP is less than 80% of baseline for greater than 4 consecutive minutes. In that case, a rescue vasopressor such as phenylephrine will be given.

Following intubation and before initial surgical incision, the BP will be checked using a non-invasive BP cuff every minute for 10 minutes. If a SBP that is less than 80% of the baseline reading is detected, the clinical team will immediately cycle the BP cuff in order to confirm the presence of hypotension. At this point an infusion of Ang II will be initiated at 2 ng/kg/min through a peripheral IV (although the recommended starting dose of Ang II is listed as 20ng/kg/min, this dosing regimen is based on patients in shock. The package insert also states that doses as low as 1.25ng/kg/min may be effective). Starting at a low dose will be important since patients taking ACE inhibitors may be more sensitive to Ang II. The BP will be checked every minute. The half-life of angiotensin 2 is < 1 minute and time to peak pharmacologic affect is less than 30-35 seconds so it will be necessary to monitor the blood pressure once per minute. The infusion will be increased at the discretion of the clinical team based on the response of the patient until a SBP within 5% of the baseline SBP has been achieved (although the rate will not be increased by more than 15ng/kg/min at a time and the rate will not exceed 80ng/kg/min based on the package insert dosing instructions). If the patient remains hypotensive despite use of the maximum dose of angiotensin II, then angiotensin II will be discontinued, the patient will be excluded from the study, and the blood pressure will be treated using conventional vasopressors. If a patient experiences SBP < 80% baseline for greater than four consecutive minutes after initiating Ang II, then a rescue vasopressor such as phenylephrine will be administered. This will be important for patients taking ARBs as they may be less sensitive to Ang II.

We will record the infusion rate of Ang II, anesthetic level (i.e. end tidal agent concentration), HR, SBP, diastolic blood pressure, mean arterial pressure, and SpO2 every minute for the duration of the study period if an infusion was initiated. Once the SBP is within 5% of baseline or greater, the infusion will be continued at that rate for 5 minutes. If the measured SBP significantly exceeds the baseline SBP by ≥15%, the infusion will be reduced or halted at the discretion of the team taking care of the patient. After 5 minutes of reaching the target pressure of within 5% of baseline or greater the final infusion rate will be recorded. At this time the third and fourth blood samples (10cc LC/MS blood sample, along with a 10 cc RIA blood sample) will be taken to measure the serum levels of different RAAS components associated with normalization of the SBP under general anesthesia. The infusion of Ang II will be discontinued. This will mark the end of the dose finding trial for the patient. Further vasopressor administration will be at the discretion of the team taking care of the patient but will not include Ang II. A fifth and final 10cc blood sample for LC/MS RAAS testing will be drawn 30 minutes after incision.

If the SBP for any enrolled patient does not drop below 80% of baseline in the first 10 minutes after intubation, Ang II will not be administered. However, we will still perform LC/MS RAAS 10 minutes after intubation, and LC/MS RAAS sampling 30 minutes after surgical incision for up to 15 previously enrolled patients as a comparison group (Arm 4). Once Arm 4 reaches 15 patients, any subsequent patients that do not experience a drop in SBP < 80% baseline will be excluded from the study and their LC/MS blood samples that were previously drawn will be discarded. However, we intend to analyze the RIA blood samples for up to 90 patients and these samples will not be discarded.

Subjects selection criteria

The study will recruit adult general surgery patients with underlying essential hypertension undergoing general anesthesia for elective general surgery. Patients will be recruited dependent upon their antihypertensive medication into the following arms.

Arm 1: Patients must be on ACE inhibitors, in addition they can also be on other classes of antihypertensive medication except for ARB.

Arm 2: Patients must be on ARBs, in addition they can also be on other classes of antihypertensive medication except for ACEi.

Arm 3: Patients on any other antihypertensive medication, and must not be on an ACEi or ARB.

Arm 4: Patients who qualify for arm 1, 2, or 3 but whose SBP does not drop below 80% of baseline in the first 10 minutes after intubation.

- **Inclusion Criteria**
    - Diagnosis of hypertension and treatment for greater than 2 months and on the following medications
        - ACE inhibitors, in addition they can also be on other classes of antihypertensive medication except for ARB
        - ARBs, in addition they can also be on other classes of antihypertensive medication except for ACEi
        - Any other antihypertensive medication, and must not be on an ACEi or ARB
    - Patients undergoing general anesthesia
    - American Society of Anesthesiologists physical status 1-3
    - Age >/= 40 given that hypertension is not prevalent below this age

- **Exclusion Criteria**
    - American Society of Anesthesiologists physical status 4-6
    - BMI > 40
    - History of deep venous thrombosis / thromboembolic disease
    - History of stroke,
    - Baseline SBP of ≥ 160 mmHg,
    - History of myocardial infarction or cardiac stents
    - Difficult airway
    - Asthma
    - Diagnosis of congestive heart failure of any stage, regardless of preserved or reduced ejection fraction; this includes both systolic heart failure and diastolic heart failure;
    - Diagnosis of chronic obstructive pulmonary disease of any stage; this includes diagnoses of chronic bronchitis and emphysema
    - Pregnant patients (safety of Ang II in pregnancy is unknown)

- Patients at increased risk for venous thromboembolic events such as current diagnosis of cancer and/or diagnosis of blood clotting disorders

- **Sample Size**
  Our goal would be to enroll and obtain data on 15 patients for each group: ACE group, ARB group, and patients on any other class of antihypertensive agent for greater than 2 months. In addition, we would like to obtain data for up to 15 patients in the comparison group (Arm 4). The sample size was chosen due to its similarity to the ATHOS II dose-finding trial.[9] It would be our intent to continue enrolling patients until a sample size of 15 patients for all 3 experimental groups has been reached. Based on an estimated incidence of hypotension of 40-60%, we expect to have to consent approximately 90 patients.[1] This is not a multisite study.

Interventions and Interactions

The largest overall commitment of time from the patient will be in the PAC at the time of recruitment. One of the PAC attendings, or investigators, or study personnel will interview the patient explain the study and attempt to recruit the patient if they are eligible. The study participant will have their questions answered. If patient agrees to participate a consent form will be electronically mailed or physically mailed, to patient. Patient will be asked to sign consent and return electronically or by physical mail. Once initial consent is received, (Giapreza) will be prepared and ready for use during surgery

On the day of surgery, the study participant will be identified in the holding area and a study representative will make sure that he or she has not changed their mind about participation and will answer any questions the study subject may have thought of since the interview in the PAC. Patient will be asked to physically sign consent in person on day of, prior to surgery. Labs will be drawn as described in the methods section.

The participant will then be taken to the OR. After appropriate monitors are placed, induction of general anesthesia will be accomplished with propofol, rocuronium, and/or succinylcholine. If there is a decrease in SBP greater or equal to 20% (as described in the methods section), Ang II will be administered starting at 2ng/kg/min. Ang II will be titrated until the SPB is within 5% of the baseline SBP (see methods section for exact details). The duration of Ang II administration will not exceed 20 minutes.

After the surgery, a study representative will see the patient in the post anesthetic recovery room (PACU) prior to discharge to evaluate for any adverse events. A follow-up phone call will also be made 7 days after the administration of angiotensin II to evaluate for any adverse events.

The LC/MS RAAS laboratory analysis will be performed by placing the patient's whole blood into a special test tube provided by La Jolla Pharmaceuticals (the tube will be identified by the patient study number and will not contain any other patient identifiers). This test tube contains an inhibitor to prevent the breakdown of some of the angiotensin metabolites, which may only be seconds. The contents of the test tube will subsequently be spun down and eventually frozen. The tubes will be sent to a specialized laboratory in Austria for analysis (Attoquant Diagnostics GmbH in Österreich, Austria). The Attoquant system will allow for quantification of the following components:

- Angiotensin I
- Angiotensin II
- Angiotensin IV
- Angiotensin 1-7
- Angiotensin 1-5
- Angiotensin 1-9

- Angiotensin 2-10
- Angiotensin 2-7
- Angiotensin 3-7
- Bradykinin 1-8
- Bradykinin 1-7
- Bradykinin 1-5
- Aldosterone

The RIA blood analysis will be performed for the following:

- Angiotensin 1-12

	Patient identified in PAC.	Patient approached in PAC and questions answered about. Patient to sign consent for study participation here.	Confirmation on day of surgery and blood draw sample in holding room and when starting IV for initial RAAS mapping	Intraoperative ang II administration, blood draws, and data collection	Patient will be evaluated in PACU for adverse events	Patient will receive a follow-up phone call 7 days after administration of angiotensin II to evaluate for adverse events
Time required of Patient	0 min	20 min	10-15 min	15-25 min	5-10 min	5 min

Outcome Measure(s)

Analytical Plan

The primary outcome will be the mean dose required to increase the SBP in these 3 cohorts with essential hypertension (ACE inhibitor, ARB, or those on another class of hypertensive agents) to within 5% of baseline or higher. 15 patients will be selected to follow suit with other similar dose finding trials with vasopressors.[10] The mean dose required to elevate SBP from the nadir to within 5% of baseline for each group will be compared for significance using a student's t-test and Bonferoni correction for multiple comparisons to determine if different doses of angiotensin 2 are required in patients chronically on ACE or ARB inhibitors. The dose-response data will be analyzed with linear regression to construct a dose response curve relating dose and percent increase in SBP from the nadir in the setting of general anesthesia. We will perform descriptive statistics on the patient population. Secondary outcomes will be the mean value for different components of the RAAS system in all 4 populations at different times prior to and during the surgical epoch;

Human Subjects Protection

Subject Recruitment Methods

Patients will be identified for participation in the Preoperative Assessment Clinic (PAC) prior to the day of surgery. Patients will be recruited by investigators and/or the study coordinator with the participation and collaboration of PAC attending and other staff present in the clinic involved in this study. We will attempt to recruit qualified subjects in a non-biased manner. Privacy will be protected because subjects will be recruited in the process of a confidential preoperative evaluation in the PAC. If they choose not participate no research record will be created other than to indicate that they declined to participate and as such there will be no contact information to destroy.

Informed Consent

Signed informed consent will be obtained from each subject. Research study members involved in the study will obtain informed consent. A copy of the signed consent will be given to the subject.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form and the sample test tubes. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed six years after closure of the study via shredding, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. In addition to the evaluation for adverse events in PACU, patients will be contacted seven days after their surgical procedure via a phone call by a study team member. The phone call will be based on the sample script and is primarily meant to evaluate if they have experienced a venous thromboembolic event due to the administration of Ang II during their surgical procedure. Any adverse reactions or events experienced by the patient as a result of Ang II administration will be followed through until their resolution, or until a determination is made that the adverse reaction is not related to the administration of Ang II.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB, La Jolla Pharmaceutical Company, or appropriate government agency if appropriate.

References

1. Comfere T, Sprung J, Kumar MM, et al. Angiotensin system inhibitors in a general surgical population. Anesthesia and analgesia 2005;100:636-44, table of contents.
2. Singh A, Antognini JF. Perioperative hypotension and myocardial ischemia: diagnostic and therapeutic approaches. Ann Card Anaesth 2011;14:127-32.
3. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. The New England journal of medicine 2017;377:419-30.
4. Ferreira AJ, Murca TM, Fraga-Silva RA, Castro CH, Raizada MK, Santos RA. New cardiovascular and pulmonary therapeutic strategies based on the Angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis. International journal of hypertension 2012;2012:147825.
5. Ferrario CM, Smith RD, Brosnihan B, et al. Effects of omapatrilat on the renin-angiotensin system in salt-sensitive hypertension. Am J Hypertens 2002;15:557-64.
6. Luque M, Martin P, Martell N, Fernandez C, Brosnihan KB, Ferrario CM. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. Journal of hypertension 1996;14:799-805.
7. Kobori H, Navar LG. Urinary Angiotensinogen as a Novel Biomarker of Intrarenal Renin-Angiotensin System in Chronic Kidney Disease. International review of thrombosis 2011;6:108-16.
8. Navar LG. Translational studies on augmentation of intratubular renin-angiotensin system in hypertension. Kidney international supplements 2013;3:321-5.
9. Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Critical Care 2014;18:534.
10. Tallarida RJ, Stone DJ, Jr., Raffa RB. Efficient designs for studying synergistic drug combinations. Life sciences 1997;61:Pl 417-25.

Appendix

1. Data Collection Form
2. Angiotensin II (Giapreza) Follow Up Telephone Questionnaire

Appendix 1: Data Collection Form

Study ID: _____

A dose finding trial for angiotensin II (Giapreza) in hypertensive adults on angiotensin converting enzyme inhibitors and angiotensin receptor blockers with anesthesia-mediated hypotension

DATA COLLECTION SHEET

Study ID: _____ Age: _____ ASA PS: _____

Gender: M / F UPT: + / - / NA

Surgery date: _____ Surgical procedure: _____

Attending Anesthesiologist: _____

Antihypertensive group: ACE / ARB / other

Antihypertensive medication: _____ Duration of therapy: _____

Preoperative creatinine: _____ Diabetes: No / NIDDM / IDDM

Peripheral vascular disease: Y / N

DVT prophylaxis: SCD / SQ heparin / SQ enoxaparin / other _____

STUDY ID: _____

1) Holding room data (Time: _____)

Vital signs	HR	
	NIBP/MAP	
	SpO_2	
Medications taken DOS		

☐ **LC/MS RAAS sample in holding**

☐ **WFBH labs--blood AND urine**

☐ **Urine NOT collected (reason): _____**

2) OR pre-induction/Baseline (Time: _____)

NIBP/MAP	

Induction

Time: _____

(1.5 mg/kg propofol, 0.8 mg/kg rocuronium; avoid pressors)

3) OR post-intubation

Time post-intubation	NIBP/MAP	Confirmatory BP (If <80% baseline)
1 min		
2 min		
3 min		
4 min		
5 min		
6 min		
7 min		
8 min		
9 min		
10 min		

IF ATII infusion started, see next page

IV fluid total PRIOR to ATII administration: _____

Time angiotensin II infusion started: _____

Goal BP +/- 5% of baseline, time reached: _____

ATII infusion at goal BP for 5 minutes, then:

VS/data	HR	
	NIBP/MAP	
	SpO_2	
	ET Isoflurane (%)	
	Final angiotensin II rate (ng/kg/min)	

☐ **LC/MS RAAS sample**

☐ **LC/MS RAAS sample 30 minutes post-incision**

Time infusion stopped: _____

IVF total AFTER ATII administration complete: _____

If no hypotension (< 80% baseline) encountered:

☐ **Move to group IV (*first 15 patients only*)**

☐ **LC/MS RAAS draw 10 minutes post-intubation**

☐ **LC/MS RAAS sample 30 minutes post-incision**

>>OR<<

☐ **Exclude patient from LC/MS analysis**

☐ **Discard first LC/MS sample from holding area**

STUDY ID: _____

Data during ATII infusion

Time post-intubation	ATII rate (ng/kg/min)	NIBP / MAP	HR	SpO2	EtCO2	ETIso (%)	ECG rhythm	Other pressor

STUDY ID: _____