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Intravenous Hydralazine for Blood Pressure Management in the Hospitalized Patient: Its Use is Often Unjustified

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Abstract

Background—Intravenous hydralazine is approved for the treatment of hypertensive emergency and widely used for hypertension associated with toxemia of pregnancy. As we had observed increased off-label use of this agent in area hospitals, we studied its use in a University teaching hospital.

Methods—Patients were identified prospectively between April and October 2010 from all hospitalized patients who had an order for intravenous hydralazine entered into the computerized physician order entry system. Clinician prescribers were unaware that this study was being conducted. Demographic and clinical information, including pre-treatment blood pressure (BP), change in BP and heart rate (HR) within 2 hours post-administration of hydralazine, concurrent and follow-up antihypertensive medications, and adverse events were obtained.

Results—There were 94 patients (mean age, 69 ± 18 years, 48% women, 89% with chronic hypertension) who received 201 intravenous hydralazine doses (mean dose of 11.4 ± 4.3 mg). Only 4 (2%) of patients had evidence of an urgent hypertensive condition (e.g., symptoms, target organ injury). Baseline BP was $175/82 \pm 25/16$ mmHg and following hydralazine was reduced by $24/9 \pm 29/15$ mmHg while HR increased by 4 ± 13 beats/min. Changes from baseline in BP were related to baseline BP: change in BP in the lower baseline range was -3 ± 20 mmHg while change observed in those with the highest range of baseline blood pressure was -35 ± 25 mmHg. Seventeen patients experienced an adverse event, the most common being hypotension ($n=11$).

Conclusions—Intravenous hydralazine is commonly prescribed for non-urgent cases of hypertension in the hospitalized patient. Changes in systolic BP, while related to baseline BP values, are nevertheless, highly variable. There is risk of hypotension associated with its use. There is evidence that this agent is not useful for many patients with hypertension in the hospital setting and may cause harm if used inappropriately.

Keywords

hydralazine intravenous; severe hypertension; hospitalized patients

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INTRODUCTION

Overly aggressive treatment of severe uncomplicated hypertension with intravenous medications is not without risk and of unproven benefit. Without evidence of acute target organ injury or hypertensive symptoms, there is no indication for parenteral medications or rapid blood pressure (BP) reduction (1,2). In fact, clinical evidence (3) and current guidelines recommend conservative management of severe hypertension without evidence of target organ damage by observation, outpatient follow-up and oral antihypertensive therapy (1,2,4). Recently published data indicate the inappropriate practice of prescribing intravenous antihypertensive medications to asymptomatic severe hypertension is a growing concern (5,6).

Intravenous hydralazine, is a potent vasodilator with a rapid onset of action that has an unpredictable effect on BP and unpredictable dose response (7–9). The approved indication for intravenous hydralazine is the management of severe hypertension when medication cannot be given orally and when there is need to urgently reduce blood pressure (10). While there is substantial evidence that the use of intravenous hydralazine for hypertensive emergency (4) and pre-eclampsia (4,11) is effective, the drug is not appropriate therapy in patients with a variety of comorbidities, including myocardial infarction, pulmonary edema and aortic dissection (10).

Anecdotal observations of overly aggressive and excessive blood pressure reductions at our institution raised concerns over a growing trend of inappropriate intravenous hydralazine use by practitioners. Similar concerns regarding indiscriminant sublingual nifedipine use were addressed at our institution over a decade ago, which revealed arbitrary treatment parameters, lack of documented target organ injury and severe adverse events (12). Although no parallels should be drawn between use of sublingual nifedipine capsules and intravenous hydralazine, the results of that study significantly altered the prescribing practices for oral nifedipine capsules within the institution. The goal of the current study was to evaluate the use of intravenous hydralazine at our institution in non-intensive care or obstetric settings including: the frequency of off-label use, the BP threshold for which the drug was ordered, the incidence, type, and severity of adverse events and the regularity of physician evaluation for parenteral antihypertensive drug requirements as well as post-treatment follow-up.

METHODS

Patient Population and Data Collection

This study was conducted at the University of Connecticut Health Center (UCHC), a teaching hospital where resident physicians write the majority of the daily orders on hospitalized patients. Study participants were identified between April and October 2010 from a daily list of all hospitalized patients who had an order for intravenous hydralazine entered into the computerized physician order entry system. The doses of intravenous hydralazine were given via a syringe pump and were diluted to 10ml with normal saline and administered over 10 to 15 minutes. Enrollment in the study included patients over 18 years old admitted to the medical and surgical non-intensive care floors and excluded those in either short-term procedural or emergency-care areas (including obstetrics-gynecology). Prescribers, patients, and nurses were unaware that the study was being conducted. Demographic and clinical information, including pre-treatment BP, change in BP from baseline, pre-treatment heart rate, and change in heart rate from baseline within 2 hours post-administration of hydralazine, concomitant antihypertensive medications were obtained. We also collected information on the incidence of adverse events, including hypotension (systolic BP <100 mmHg or documentation of episode of orthostasis (reduction

in systolic BP > 20 mmHg with symptoms), dizziness/lightheadedness, palpitations, syncope, nausea, diaphoresis, and chest pain. Evidence of hypertensive emergency included documented target organ injury (elevated cardiac enzymes, pulmonary edema, encephalopathy, acute renal insufficiency) or symptoms consistent with severe hypertension (including moderate/severe headache, shortness of breath, chest pain/pressure or altered vision). All aspects of the study were approved by the University of Connecticut Health Center (UCHC) Institutional Review Board, with a waiver of informed consent.

Statistical Analysis

Analyses were performed on all patients included who received at least one dose of intravenous hydralazine during the study period. To assess the association between pre-treatment systolic BP and change in systolic BP, patients were divided into four ranges based on pre-treatment systolic BP. Differences between the changes in systolic BP amongst the individual ranges were compared using a paired *t*-test.

Current guidelines recommend that patients with hypertensive emergency avoid reductions in systolic BP greater than 25% within 2 hours of drug administration (2). Hence, differences in all baseline and clinical characteristics were compared between those patients who did versus did not achieve a greater than 25% reduction in their systolic BP within 2 hours from receiving intravenous hydralazine using either a Chi-squared or paired *t*-test. Those with a $p < 0.05$ on univariate analysis were then entered into a backwards, stepwise multivariate logistic regression model. The following variables were included in the multivariate model: age (years), history of hypertension, history of arrhythmia, prior use of either angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), prior use of an alpha-blocker, prior use of at least 3 drugs for treating hypertension, and pre-treatment systolic BP. A p -value < 0.05 was considered significant in the multivariate logistic regression model. Adjusted odds ratios, 95% confidence intervals, and 2-tailed p values were calculated. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 201 doses of intravenous hydralazine (mean dose, 11.4 ± 4.3 mg) were administered to 94 hospitalized patients during the study period. The characteristics of the patients are shown in Table 1. Most patients had a history of hypertension and were treated prior to admission with various anti-hypertensive drugs. Only 4 (2%) patients had evidence of hypertensive emergency (symptoms, probable target organ injury) reported. Approximately half (49%) of the doses administered were ordered as one-time urgent doses and 48% of the doses were ordered between 11 pm and 7am. The internal medicine service ordered 52% of the intravenous hydralazine doses and overall 82% were prescribed by physicians-in-training. Seven (7.5%) patients were evaluated by a physician prior to hydralazine administration and 17 (18%) were evaluated post-dosing.

The mean BP prior to administration of intravenous hydralazine was $175/82 \pm 25/16$ mmHg. The distributions of the pre-treatment systolic and diastolic BPs resulting in intravenous hydralazine administration are shown in Figure 1. During the 2 hours following intravenous hydralazine administration, the BP was reduced by a mean of $24/9 \pm 29/15$ mmHg while heart rate increased by 4 ± 13 beats/min (note: 59% of patients were on a beta-adrenergic blocking agent). Of the 201 intravenous hydralazine doses administered, a majority (83%) resulted in $< 25\%$ reduction in systolic BP. Adjustments of long-acting oral medications were made in 24 (25%) patients within 24 hours of intravenous hydralazine dosing. There were 16 adverse events (8.0% of doses) in 16 patients recorded following intravenous hydralazine administration. Most of these adverse events (69%) were hypotension, with a

few patients developing symptoms of dizziness/lightheadedness. Patients with hypotension had reductions in systolic BP ranging from -27 to -100 mmHg from pre-treatment, including 6 patients who had greater than a 65 mmHg reduction. Those reporting symptoms of dizziness/lightheadedness had reductions in systolic BP of -20 to -26 mmHg from pre-treatment.

Changes from pre-treatment in BP were evaluated according to the ranges of baseline BP (Table 2). Patients with a pre-treatment systolic BP of ≤ 164 mmHg (the lowest range) experienced modest reductions in BP (-3 ± 20 mmHg) while more marked changes were observed in those with the highest range (≥ 190 mmHg) of pre-treatment systolic BP (-35 ± 25 mmHg). The changes in BP in the lowest pre-treatment range were significantly smaller than any of the three higher ranges ($p < 0.0001$ for all). The variance in changes in BP was large and overlapping in all the ranges.

Multivariate logistic regression demonstrated that patients with a history of arrhythmias ($p = 0.021$) and prior use of either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) ($p = 0.030$) were significantly more likely to have a greater than 25% reduction in systolic BP following administration of intravenous hydralazine (Table 3). Furthermore, a higher pre-administration systolic BP was also significantly associated with a $> 25\%$ reduction in systolic BP ($p = 0.017$).

DISCUSSION

Our study demonstrated that parenteral hydralazine is often being prescribed indiscriminately for asymptomatic moderate to severe hypertension without evidence of symptoms or target organ injury. Recently published data from other centers show that this practice is not limited to one institution (5,6,13). Our study was not able to address the clinical decision making behind the choice of intravenous hydralazine, but it is likely that its indiscriminate use is associated with unfamiliarity of physicians and nursing staff with current guidelines for the management of asymptomatic hypertension versus hypertensive emergencies coupled with a desire among physicians and nurses to achieve lower BPs in hospitalized patients (despite a lack of evidence supporting this practice). Our data also demonstrated that parenteral hydralazine is most commonly prescribed for a single elevated BP without first adjusting long-acting medications, indicating that the physicians and nursing staff are treating a “number” rather than the complete clinical situation. Interestingly the majority of the patients (83%) who received intravenous hydralazine experienced less than the recommended 25% reduction in BP for the treatment of hypertensive emergency. Our data are supported by findings from the Study Treatment of Acute Hypertension (STAT) trial that showed when intravenous hydralazine was used as a first-line therapy for hypertensive emergency; it frequently failed to achieve the target BP reduction (13). It appears that common use of parenteral hydralazine use is occurring because the agent is perceived as a “benign” medication with an acceptable adverse-effect profile, much like the perception of sublingual nifedipine over a decade ago (12). However, as demonstrated by our study results, there can be excessive reductions in BP that may potentially result in adverse outcomes including hypotensive symptoms and reflex tachycardia. While there were no irreversible adverse drug events (e.g. stroke) during the course of our study, our sample may be too small to detect more severe and infrequent consequences of severe BP reductions.

While our data demonstrate a relationship between pre-treatment BP values and response to parenteral hydralazine, the effects were not always predictable even in those with the highest pre-treatment BPs. Our data agree with previous studies demonstrating the unpredictable response of intravenous hydralazine that may be associated with highly variable

pharmacodynamics (7–9). We did identify certain clinical factors that predicted a greater response to intravenous hydralazine including history of arrhythmia and concurrent use of blockers of the renin-angiotensin system. Because the exact mechanism of action of hydralazine is unclear other than systemic vasodilation, it is difficult to associate causality with these correlations. The relationship between intravenous hydralazine and blockers of the renin-angiotensin system is one that is speculative at this time and requires further investigation.

The most worrisome finding in this study was the lack of prescriber evaluation prior to ordering a parenteral drug for patients who had asymptomatic hypertension, which in some cases were only moderately elevated. Patients were not routinely evaluated for evidence of a true hypertensive emergency with target organ injury or other potential causes of elevated BPs in the hospital such as pain, anxiety or respiratory distress. Our plan therefore is to initiate education on the results of this study via quality improvement discussions in the area teaching hospitals as it is clear that physician-in-training and nursing knowledge on the guidelines for the treatment of asymptomatic moderate and severe hypertension in hospital inpatients is lacking.

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Figure 1.
Threshold blood pressure values for intravenous hydralazine dosing in hospitalized patients
(Upper panel, systolic BP and lower panel, diastolic BP)

Table 1**Baseline Characteristics of Hospitalized Patients**

No. of Patients	94
Age (years)	68.6 ± 17.9
Females	45 (47.9 %)
Hospital length of stay (days)	8.3 ± 8.6
Past Medical History	
Hypertension	84 (89.4 %)
Diabetes	30 (31.9 %)
Coronary Artery Disease	25 (26.6 %)
Chronic Kidney Disease	27 (28.7 %)
Arrhythmias	14 (14.9 %)
Obstructive Sleep Apnea	7 (7.4 %)
Stroke/TIA	16 (17.0 %)
Congestive Heart Failure	11 (11.7 %)
Medications prior to admission	
Beta-Blockers	55 (58.5 %)
Calcium antagonists	35 (37.2 %)
Renin-Angiotensin Blockers	53 (56.4 %)
Diuretics	37 (39.4 %)
Alpha-Blocker	13 (13.8 %)
Central Acting Agent	7 (7.4 %)
Nitrates	10 (10.6 %)
Hydralazine (oral)	6 (6.4 %)
Aldosterone Antagonist	1 (1.1 %)

* Data provided as n (%) or mean ± SD based on number of patients included (n=94).

Table 2**Blood Pressure Reductions by Quartile**

Inter-Quartile Baseline Systolic BP Range (mmHg)	Change in Systolic BP (mean±SD)	p-values between quartiles (Pearson Correlation)
1. ≤ 164 (n=49, 24.4 %)	−2.6 ± 20.0	
2. 165–179 (n=48, 23.9 %)	−24.9 ± 24.2	p<0.0001 vs. 1 (
3. 180–189 (n=48, 23.9 %)	−30.9 ± 10.5	p<0.0001 vs. 1
4. ≥ 190 (n=56, 27.9 %)	−35.4 ± 24.9	p<0.0001 vs. 1 p=0.03 vs. 2

SD = standard deviation

Table 3

Multivariate Logistic Regression – Predictors of a large response (>25% reduction in SBP from baseline)

Variable	OR (95% CI)	p-value
Age (years)	1.003 (0.97–1.038)	0.840
History of hypertension	2.79 (0.49–15.73)	0.246
History of arrhythmias	0.147 (0.029–0.751)	0.021
Prior ACE/ARB use	4.82 (1.16–19.98)	0.030
Prior alpha-blocker use	N/A	0.998
History of ≥ 3 drugs for hypertension	1.19 (0.97–1.038)	0.840
Pre-administration of hydralazinesystolicBP	1.053 (1.009–1.099)	0.017

ACE = angiotensin converting enzyme inhibitor; OR = adjusted odds ratio; ARB = angiotensin receptor blocker; CI = confidence interval; N/A = not available