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National Survey of Acute Hypertension Management

Jessica E. Benson, Anthony T. Gerlach, Joseph F. Dasta

Abstract

***Background*: National practice guidelines do not exist for the treatment of acute hypertension (AH) in the critically ill adult. An initial step towards guideline development is to document current prescribing patterns of intravenous (IV) antihypertensives for AH, which serves as the purpose of this survey.**

***Methods*: An e-mail to participate in this Web-based survey was sent to 5574 critical care physician and pharmacist members of the Society of Critical Care Medicine and the American College of Clinical Pharmacy. The survey, which requested responses concerning antihypertensive management in the respondents' intensive care unit (ICU), opened March 12, 2007 and closed May 11, 2007.**

***Results*: Three hundred ninety three (7.1%) responses were returned; 25 were excluded. The most common practice setting (44.6%) was a mixed-population ICU. One hundred three (28.3%) respondents reported that a guideline exists in their institution for the treatment of hypertensive emergency (HE) in acute hemorrhagic stroke (AHS), while only 30 (8.2%) had guidelines for the non-stroke (NS) patient. Among physician respondents, mean systolic blood pressures (SBP) used to initiate IV antihypertensives were 180.9 (range 105-220) mm Hg and 167.2 (range 100-220) mm Hg in NS and AHS patients, respectively. In the NS patient, intermittent IV labetalol was the drug of choice among physicians (21.3%) and pharmacists (26.5%), while nicardipine was the drug of choice for the AHS patient (34.7%, 36.2% respectively). The second line agent of choice for the NS patient was sodium nitroprusside among physicians (19.8%) and continuous infusion labetalol for pharmacists (19.8%). For the AHS patient, the second line agent of choice was nicardipine among physicians (21.8%) and pharmacists (27.6%). One hundred thirty one (36%) respondents reported that they have seen a patient with symptomatic cyanide and/or thiocyanate toxicity.**

***Conclusions*: Because most institutions do not have HE guidelines, our data described herein provides the rationale for developing a national guideline.**

Key words: hypertension, hypertensive crisis, hypotensive agents, toxicity

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Introduction

Variability in the care of the critically ill can be introduced on many levels. Practice inconsistencies may exist between individual practitioners, specific intensive care units (ICU), or between hospitals. Practice guidelines are developed so patients may benefit from an evidence-based, standardized approach to patient care. This minimizes practice variability between and within patients. Guidelines

are developed by grading the quality of studies and generating a recommendation based on that evidence. For the critically ill patient, examples of these efforts are the recently published guidelines for sedation [1] and severe sepsis [2].

Currently, no national practice guideline exists for the treatment of acute hypertension in the critically ill patient except for recommendations in ischemic stroke patients [3,4]. We believe that one of the first steps towards standardizing pharmacotherapy of the patient with acute hypertension is to document the way that intravenous (IV) antihypertensives are selected and used. These findings will also establish where educational efforts should be focused.

The primary objective of this study is to characterize how IV antihypertensive agents are used in the management of hypertensive emergency. Secondary objectives were to determine the number of hospitals with acute hypertension guidelines and to describe the incidence of adverse drug events associated with these agents.

Materials and methods

Following the Institutional Review Board approval in December 2006, an e-mail to participate in this Web-based survey (www.zoomerang.com) was sent to 4204 critical care physician and 1370 pharmacist members of the Society of Critical Care Medicine (SCCM) and the American College of Clinical Pharmacy (ACCP). Within SCCM, the survey was sent to the Anesthesia, Internal Medicine, Neuroscience, Surgery, and Clinical Pharmacy and Pharmacology sections of the organization. Within ACCP, the survey was sent to the Critical Care Practice Research Network (Critical Care-PRN).

Two versions of the survey were developed to address the practice patterns of the individual practitioner (pharmacist or physician). Physician respondents were asked to answer questions based on their own practice patterns while pharmacist respondents were asked to answer questions based on the practice pattern within their ICU. Hypertensive emergency was defined as per the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines [5]. These guidelines define hypertensive emergency as a severe elevation in blood pressure (>180/120 mmHg) complicated by evidence of impending or progressive organ dysfunction. The survey consisted of four sections: demographics (11 questions), non-stroke (NS) patient (5 questions), acute hemorrhagic stroke (AHS) patient (5 questions), adverse drug events (6 questions), with an estimated completion time of approximately 10-15 minutes. The questionnaire was reviewed for face validity by four pharmacists and revised. The survey opened March 12, 2007 and closed May 11, 2007. One reminder email was sent to all participants during the survey period. A survey was excluded if it was less than 75% complete, from a pediatric ICU, or was from a respondent not in active ICU practice.

The survey responses were downloaded from the website into Microsoft Excel (Microsoft Corporation, Redmond, OR), and data analysis was completed via Microsoft Excel and SPSS, version 14.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used in the analysis. Where respondents indicated a range of numbers to a question that asked for a specific number, the median of the range was used.

Results

A. Demographics

Two-hundred forty-three (5.8%) physician and 150 (10.9%) pharmacist responses were returned for an overall response rate of 7.1%. Twenty five surveys were excluded (15 were <75% complete, 6 were from a non-ICU area of practice, and 4 were from a pediatric ICU). The majority of respondents practice in an academic medical center (73.4%) (**Table 1**). Most institutions were non-profit organizations (91.0%). Over one-fourth of respondents practice in an institution with 401-600 beds and most reported they practice in a general (mixed) patient population ICU (44.6%).

Physicians and pharmacists reported that they practice in an ICU with 25.2±21.2 (mean±SD) and 23.4±14.9 beds, respectively. Each group also estimated that 4.9±6.8 and 6.3±9.0 patients were admitted with hypertensive emergency to their unit per month, while a similar number of patients develop hypertensive emergency during their ICU stay (4.4±7.0 and 4.8±6.3 per month, respectively) (**Table 2**).

B. Non-stroke patient

Only 10.3% of physicians and 4.5% of pharmacists reported that a practice guideline or protocol exists in their institution for the treatment of hypertensive emergency in the non-stroke patient (**Figure 1**). Intermittent IV labetalol was the drug of choice among physicians and pharmacists (**Table 3**). If the first-line agent failed to yield acceptable outcomes, the physician-preferred second line agent was sodium nitroprusside while pharmacists most frequently chose continuous infusion labetalol as their second-line agent of choice (**Table 4**).

Respondents were asked what blood pressure is used to trigger initiation of IV antihypertensive therapy. Physician and pharmacist responses were similar (**Table 5**). One-hundred ninety-one physicians reported a systolic blood pressure (SBP) category, while only 130 reported using a mean arterial pressure (MAP). There was a large standard deviation in the blood pressure trigger. Fewer pharmacists reported a MAP (n =26) than those that reported a SBP (n =117). Fifty-nine percent of respondents indicated the total duration of IV antihypertensives most often required is 24-48 hours.

C. Acute hemorrhagic stroke patient

Twenty-six percent of physician respondents and 32% of pharmacists reported that a practice guideline or protocol exists in their institution for the treatment of hypertensive emergency in a patient with acute hemorrhagic stroke (**Figure 1**). Nicardipine was the drug of choice among physicians and pharmacists (**Table 3,4**).

As in the non-stroke patient, physician and pharmacist responses were similar in regards to blood pressure triggers (**Table 5**). One-hundred seventy-four physicians reported a systolic blood pressure (SBP), while only 110 reported using a MAP. There was also a large standard deviation in the blood pressure trigger. Fewer pharmacists also reported a MAP (n =22) than those that reported a SBP (n =96). Forty-six percent of respondents indicated the total duration of IV antihypertensives most often required is 24-48 hours.

D. Adverse events

Physicians (59.4%) and pharmacists (57.5%) uniformly reported that hydralazine is the drug most likely to cause tachycardia (**Table 6**) and that sodium nitroprusside is the drug most likely to cause a precipitous fall in blood pressure (**Table 7**). The majority (57.1%) of respondents reported that in their opinion, the incidence of cyanide and/or thiocyanate toxicity with the use of sodium nitroprusside is <1% while 43.7% of physicians and 32.3% of pharmacists reported that they personally witnessed a patient with cyanide and/or thiocyanate toxicity while receiving sodium nitroprusside.

Discussion

These data might provide critical care practitioners with insight into the current treatment of hypertensive emergency. There was considerable similarity between pharmacist responses, from the perspective of their ICU, and physician responses from the perspective of their individual preferences. Although there are more guidelines in patients with stroke, our results indicate that there is a general lack of guidelines for acute hypertension among many individual institutions. This is likely related to the published recommendations from the Stroke Society [3,4]. Not having national guidelines is reflected by the variability in the first and second-line choices of drug to use in the management of hypertensive emergency and the wide range of threshold blood pressures. The first-line agents of choice for both the non-stroke and acute hemorrhagic

stroke patient each had <50% of respondents select that agent. Even before a first-line agent is chosen, establishing the most appropriate blood pressure trigger to initiate treatment is not consistent. A wide range of threshold values was reported, which was reflected by one standard deviation of at least 20 mmHg for a MAP or SBP. More physicians and pharmacists reported using a SBP measurement to guide their therapy, but approximately one-third still reported a MAP.

There are a wide variety of agents to choose from to treat hypertensive emergencies. Little recent information has been published on the topic. Two recent review articles provide background information on the various drugs available [6,7]. For example, labetalol is commonly used but it should not be used in patients with acute heart failure, reactive airway disease, or heart block. Hydralazine has variable onset and offset times, and can cause reflex tachycardia unless the patient is receiving a concurrent beta-blocker. Nicardipine, a dihydropyridine calcium-channel blocker, has become an increasingly popular drug and our survey reports it being the drug of choice for acute hemorrhagic stroke. In the non-stroke patient, it is the second-line drug for physicians and third-line by pharmacists. While it is a safe drug, its duration of action of 4-6 hours is consistent with its long elimination half-life. A recent study evaluated blood pressure response in 47 patients with hypertensive emergency and who received at least 30 minutes of a continuous infusion of an IV antihypertensive [8]. Twenty-one patients received IV nicardipine, 18 received nitroprusside, five were prescribed nitroglycerin, two received esmolol, and one received diltiazem. Only 32% of patients achieved their goal blood pressure of a MAP reduction of 10-25%. Patients treated with nicardipine had a greater risk of excessive MAP reduction than any other agent. In fact, all patients receiving nicardipine developed hypotension and 78% of patients receiving nitroprusside were hypotensive. Perhaps this excessively high percent of patients developing hypotension from nicardipine was due to too frequent dosage adjustments with this drug. Further studies are needed to test this hypothesis.

Of note, over half of respondents reported that in their opinion, the incidence of cyanide and/or thiocyanate toxicity with the use of sodium nitroprusside is <1%, yet a third of respondents reported that they had witnessed a case of toxicity. This may call into question the actual versus perceived or reported incidence of toxicity with this drug. Cyanide and thiocyanate toxicity is well described with this agent, particularly in patients with renal insufficiency receiving moderately low doses [6]. Furthermore, a recent study showed that hemolyzed blood and plasma-free hemoglobin during cardiopulmonary bypass accelerates the release of free cyanide from sodium nitroprusside, thus increasing the risk of toxicity in these patients receiving sodium nitroprusside [9].The symptoms of cyanide and thiocyanate toxicity such as confusion, agitation, hallucinations, metabolic acidosis, for example, commonly occur in ICU patients, thus diagnosing drug toxicity may be difficult with this agent.

Each available drug has strengths and weaknesses. An ideal agent does not exist. A new agent, recently approved for use in the US is clevidipine, a dihydropyridine calcium-channel blocker like nicardipine. Unlike nicardipine, clevidipine is metabolized by plasma and tissue esterases and has an elimination half life of 1-2 minutes [10]. A recently published clinical trial with this agent in patients with acute severe hypertension (>180/>115 mmHg) received clevidipine starting at 2 mg/hr and titrated as needed every 3 minutes up to 32 mg/hr [11]. Within 30 minutes, 89% of patients achieved the target blood pressure and median time to achieve this target range was 11 minutes.

Limitations of this study include our gathering opinion data, rather than actual use data in the treatment of acute hypertension. However, the similarity between opinions of critical care pharmacists and physicians is an interesting finding. The results of the ongoing STAT trial (Studying the Treatment of Acute hyperTension) may provide a perspective of actual use data [12]. STAT is a multicenter observational registry of patients with acute severe hypertension treated with IV antihypertensive therapy in a critical care setting. STAT will have data on 1500 consecutive patients from 25 U.S. hospitals. Interesting preliminary findings of STAT indicate 84% of patients had end-organ injury at

presentation, the 90 day mortality rate was 6.4%, and 31% of patients were re-hospitalized by 90 days.

We also note that there is selection bias that results from a survey directed towards critical care practitioners who are members of professional organizations. It also should be noted that the survey had a low response rate, and may not be a true representation of the majority of critical care practitioners.

We hope that these results may provide background information for a potential new practice guideline for the treatment of acute hypertension in the critically ill patient. These data can also be used to reveal educational deficiencies and hence provide the opportunity to focus educational efforts on common misconceptions in therapeutics. Perhaps more education on the adverse drug events associated with IV antihypertensives is needed. The variable goal blood pressures and numerous drugs selected as first and second-line provides the scientific basis for the desperate need for guidelines on acute hypertension from a national organization.

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At the time of completion of this project, Dr. Benson was a Critical Care Pharmacy Resident at The Ohio State University and Professor Dasta was on faculty at The Ohio State University. All work was conducted at The Ohio State University.

Table 1. DEMOGRAPHIC QUESTIONS AND RESPONSES

Demographic	Physician Survey	Pharmacist Survey	Overall
	No. Respondents (% Reporting)		
In regards to teaching, what best describes the hospital in which you practice?			
Medical school affiliation	179 (77.2)	89 (66.9)	268 (73.4)
No medical school affiliation	53 (22.8)	44 (33.1)	97 (26.6)
Which of the following best describes the hospital in which you practice?			
Not-for-profit hospital	212 (91.4)	121 (90.3)	333 (91.0)
For-profit	20 (8.6)	13 (9.7)	33 (9.0)
How many licensed beds are in the hospital in which you practice?			
0-200	24 (10.3)	8 (6.0)	32 (8.7)
201-400	62 (26.5)	37 (27.6)	99 (26.9)
401-600	72 (30.8)	32 (23.9)	104 (28.3)
601-800	39 (16.7)	29 (21.6)	68 (18.5)
>800	37 (15.8)	28 (20.9)	65 (17.7)
What is the primary type of ICU in which you practice?			
Burn	2 (0.9)	0 (0)	2 (0.5)
Cardiothoracic	14 (6.0)	2 (1.5)	16 (4.3)
Coronary Care Unit	1 (0.4)	6 (4.5)	7 (1.9)
General (mixed)	113 (48.5)	51 (38.1)	164 (44.6)
Medical	37 (15.9)	40 (29.9)	77 (20.9)
Neurosurgical	15 (6.4)	8 (6.0)	23 (6.2)
Pulmonary	0 (0)	1 (0.7)	1 (0.3)
Surgical	35 (15.4)	13 (9.7)	48 (13.0)
Transplant/BMT	1 (0.4)	0 (0)	1 (0.3)
Trauma	15 (6.4)	13 (9.7)	28 (7.6)

*Responses reported as n (%)

Table 2. PERCEIVED INCIDENCE OF HYPERTENSIVE EMERGENCY

	Physician Survey	Pharmacist Survey
How many licensed beds are in the ICU in which you practice?	25.2±21.2	23.4±14.9
How many patients do you estimate are admitted with hypertensive emergency in your unit on a per month basis?	4.9±6.8	6.3±9.0
How many patients do you estimate develop hypertensive emergency on a per month basis while they are in the ICU?	4.4±7.0	4.8±6.3

*Responses reported as mean±standard deviation (SD)

Table 3. PHARMACOLOGIC AGENT OF CHOICE

Non-stroke Patient			
Physician		**Pharmacist**	
Labetalol – intermittent	49 (21.3)	Labetalol – intermittent	35 (26.5)
Nicardipine	45 (19.6)	Sodium nitroprusside	35 (26.5)
Sodium nitroprusside	43 (18.7)	Nicardipine	22 (16.7)
Labetalol – continuous	34 (14.8)	Labetalol – continuous	12 (9.1)
Esmolol	18 (7.8)	Nitroglycerin	9 (6.8)
Metoprolol	14 (6.1)	Hydralazine	6 (4.5)
Nitroglycerin	11 (4.8)	Metoprolol	6 (4.5)
Hydralazine	8 (3.5)	Enalaprilat	3 (2.3)
Enalaprilat	7 (3.0)	Esmolol	3 (2.3)
Fenoldopam	1 (0.4)	Fenoldopam	1 (0.8)
Acute Hemorrhagic Stroke Patient			
Nicardipine	76 (34.7)	Nicardipine	42 (36.2)
Labetalol – continuous	46 (21.0)	Labetalol – intermittent	34 (29.3)
Sodium nitroprusside	36 (16.4)	Sodium nitroprusside	19 (16.4)
Labetalol – intermittent	32 (14.6)	Labetalol – continuous	15 (12.9)
Esmolol	12 (5.5)	Nitroglycerin	3 (2.6)
Metoprolol	6 (2.7)	Hydralazine	2 (1.7)
Hydralazine	4 (1.8)	Esmolol	1 (0.9)
Nitroglycerin	3 (1.4)	-	
Enalaprilat	3 (1.4)	-	
Urapidil	1 (0.5)	-	

*Responses reported as n (%)

Table 4. SECOND LINE PHARMACOLOGIC AGENT

Non-stroke Patient			
Physician		**Pharmacist**	
Sodium nitroprusside	45 (19.8)	Labetalol – continuous	26 (19.8)
Nicardipine	39 (17.2)	Sodium nitroprusside	23 (17.6)
Labetalol – continuous	37 (16.3)	Labetalol – intermittent	20 (15.3)
Labetalol – intermittent	30 (13.2)	Nicardipine	19 (14.5)
Hydralazine	24 (10.6)	Hydralazine	13 (9.9)
Enalaprilat	17 (7.5)	Metoprolol	11 (8.4)
Esmolol	13 (5.7)	Esmolol	8 (6.1)
Nitroglycerin	11 (4.8)	Nitroglycerin	7 (5.3)
Metoprolol	8 (3.5)	Enalaprilat	4 (3.1)
Fenoldopam	3 (1.3)	-	
Acute Hemorrhagic Stroke Patient			
Nicardipine	48 (21.8)	Nicardipine	32 (27.6)
Labetalol – continuous	45 (20.5)	Labetalol – continuous	28 (24.1)
Sodium nitroprusside	33 (15.0)	Labetalol – intermittent	21 (18.1)
Labetalol – intermittent	24 (10.9)	Sodium nitroprusside	14 (4.0)
Hydralazine	20 (9.1)	Hydralazine	6 (5.0)
Enalaprilat	15 (6.8)	Esmolol	5 (4.3)
Esmolol	13 (5.9)	Enalaprilat	4 (3.4)
Nitroglycerin	10 (4.5)	Metoprolol	3 (2.6)
Metoprolol	7 (3.2)	Nitroglycerin	3 (2.6)
Fenoldopam	4 (10)	-	

*Responses reported as n (%)

Table 5. BLOOD PRESSURE VALUES TO TRIGGER IV ANTIHYPERTENSIVE THERAPY

	Physician (mean±SD mmHg) (n =number of responses*)	**Pharmacist** (mean±SD mmHg) (n =number of responses*)
Non-stroke	MAP 119.1±24.3 n =130	MAP 111.0±22.3 n =26
	SBP 180.9±21.8 n =191	SBP 177.6±22.9 n =117
Acute hemorrhagic stroke	MAP 116.3±26.1 n =110	MAP 113.9±23.3 n =22
	SBP 167.2±22.2 n =174	SBP 167.0±21.9 n =96

* Respondents were given the option to free-text either a mean arterial pressure (MAP) or a systolic blood pressure (SBP) trigger based on what they most commonly use in practice

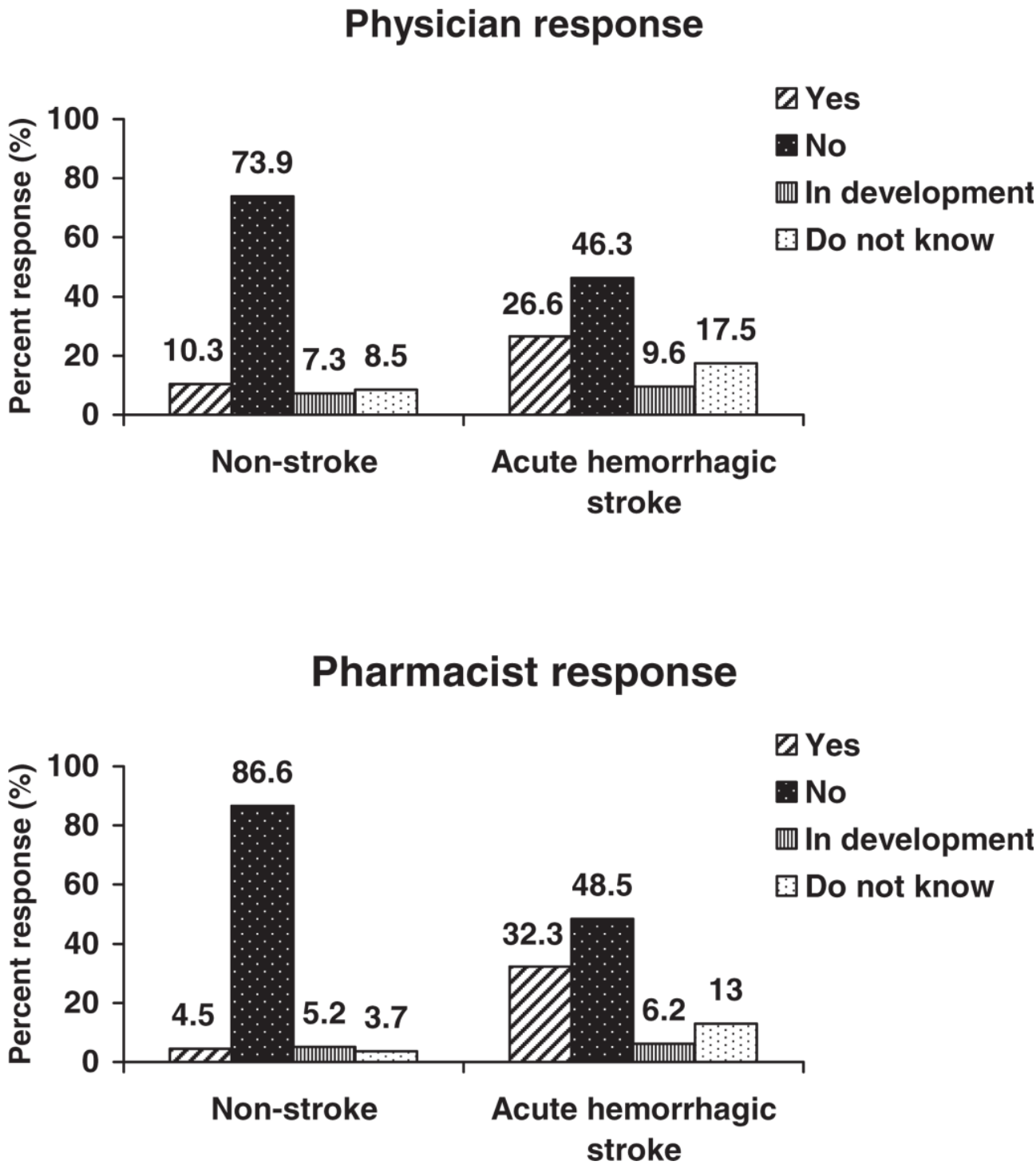
Table 6. THE DRUG MOST LIKELY TO CAUSE TACHYCARDIA

Physician Response	n (%)	**Pharmacist Response**	n (%)
Hydralazine	133 (59.4)	Hydralazine	73 (57.5)
Sodium nitroprusside	57 (25.4)	Sodium nitroprusside	18 (14.2)
Nitroglycerin	20 (8.9)	Nicardipine	13 (10.2)
Nicardipine	8 (3.4)	Nitroglycerin	10 (7.9)
Fenoldopam	3 (1.3)	Fenoldopam	7 (5.5)
Enalaprilat	2 (0.9)	Enalaprilat	3 (2.4)
Metoprolol	1 (0.4)	Labetalol	3 (2.4)

Table 7. THE DRUG MOST LIKELY TO CAUSE PRECIPITOUS FALL IN BLOOD PRESSURE

Physician Response	n (%)	**Pharmacist Response**	n (%)
Sodium nitroprusside	132 (56.9)	Sodium nitroprusside	54 (42.5)
Hydralazine	24 (10.3)	Hydralazine	20 (15.7)
Enalaprilat	16 (6.9)	Enalaprilat	15 (11.8)
Nitroglycerin	15 (6.5)	Esmolol	7 (5.5)
Nicardipine	10 (4.3)	Labetalol - intermittent	7 (5.5)
Esmolol	9 (3.9)	Nitroglycerin	6 (4.7)
Labetalol – continuous	6 (2.6)	Metoprolol	6 (4.7)
Nifedipine	6 (2.6)	Labetalol – continuous	5 (3.9)
Fenoldopam	5 (2.2)	Nicardipine	4 (3.1)
Labetalol – intermittent	5 (2.2)	Fenoldopam	3 (2.4)
Metoprolol	4 (1.7)	-	-

Figure 1. PRACTICE GUIDELINE FOR THE TREATMENT OF HYPERTENSIVE EMERGENCY IN RESPONDENTS' INSTITUTION



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