Original Paper

Treatment of Hypertension in the Inpatient Setting: Use of Intravenous Labetalol and Hydralazine

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*Acute blood pressure elevations are commonly treated in hospitalized patients. There are no guidelines for appropriate practice and no evidence that such treatment is useful. The authors performed a retrospective review of medical and pharmacy records to determine how often intravenous hydralazine and labetalol are ordered and administered. During a 1-year study period, a total of 29,545 hospitalizations were recorded. The authors identified 2189 patients (7.4% of all patients) for whom 7242 orders were written for hydralazine as needed (10–20 mg per dose) and 5915 for labetalol (10–20 mg per dose). Ordered drugs were adminstered in 60.3% of patients, and the average number of doses administered was 5.3±8.2 (mean ± SD) for hydralazine and 5.6±7.7 for labetalol. Hospital length of stay (LOS) for patients for whom hydralazine was ordered was 12.0±15.9 days for those who received at least 1 dose and 7.1±9.0 days for those who did not receive a dose (*P*<.001). For patients for whom labetalol was ordered, patients receiving at least 1 dose had an LOS of 11.8±16.1 days vs 7.9±10.4 days for those who did not receive a dose (*P*<.001). Treatment of elevated blood pressure in in-patients is a common practice. The authors suggest that evidence is needed to determine whether the practice is of benefit.* J Clin Hypertens (Greenwich). *2010;12:29–33.* ©*2009 Wiley Periodicals, Inc.*

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The practice of lowering blood pressure (BP) acutely in "hypertensive urgencies" (generally defined as sustained BP elevations above the range of 110–120 mm Hg diastolic or 180–200 mm Hg systolic without associated ongoing target organ damage) and "emergencies" (similarly elevated BPs associated with target organ damage) is well accepted. However, recent literature reviews have failed to demonstrate a clear benefit,[1,2] and attempts to lower BP may result in hypotension, which can cause adverse cardiovascular events.[3–5]

Much more commonly encountered in in-patient settings are nonsustained transient elevations of BP to the range of "urgency," and many physicians routinely treat these acute elevations of BP in hospitalized patients with antihypertensives. Guidelines for hypertension treatment[6–9] are silent on the issue of in-patient management of hypertension, and there is no expert consensus recommendation to our knowledge.

To begin an assessment of current practices related to treatment of in-patient hypertension, we undertook an analysis of the use of intravenous antihypertensives in patients admitted to the University of Michigan Hospital with primary diagnoses other than hypertension. In this initial effort, we focused on the use of intravenous low-dose

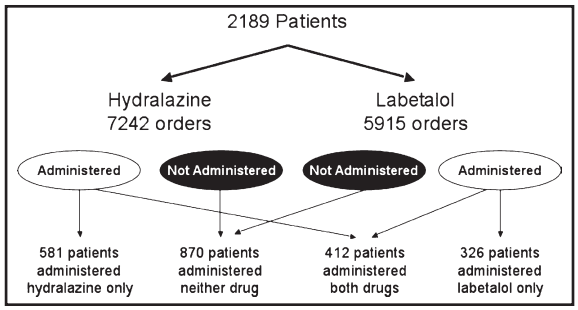

Figure. Intravenous hydralazine and labetalol: pharmacy orders and drug administration in hospitalized patients.

hydralazine (10–20 mg) and labetalol (10–20 mg), the two agents commonly employed in our hospital for the treatment of hypertension that are not routinely used for other conditions.

METHODS

The study was approved by the University of Michigan institutional review board for human research and met all Health Insurance Portability and Accountability Act requirements.

Study Sample

A query of the hospital's electronic data warehouse was made to identify all patients 18 years and older admitted to the University of Michigan Medical Center from October 1, 2007, through September 30, 2008. Each separate admission during the study period was counted as an event for patients with multiple admissions. Patient characteristics obtained included age, sex, and hospital length of stay (LOS). Patients for whom intravenous labetalol and/or hydralazine orders were entered into the hospital's pharmacy system were identified for study. Patients with principal diagnoses of hypertension, ie, those admitted specifically for treatment of hypertension, were excluded (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 401.0, 401.1, 401.9, 405.0). We also determined which patients had admission diagnoses corresponding to accepted indications for aggressive antihypertensive therapy if necessary[10]: *ICD-9* codes 437.2 (hypertensive encephalopathy), 436 (cerebral vascular accident/cerebral infarction), 430, 431, 432.0 to 432.9 (subarachnoid hemorrhage), 428.1 (acute left ventricular dysfunction), 506.1, 518.4 (acute pulmonary edema), and 441.0 to 441.3 (aortic dissection). We did not include preeclampsia in this analysis.

Medication data included identification of all orders written and entered into the hospital pharmacy system, including the name of the medication, directions for frequency of use, and the number of doses administered during the hospital stay.

Analysis

Descriptive statistics of mean and standard deviation (SD) for continuous variables and frequency with percent for categoric data were used to describe the sample characteristics. Comparisons of the use of specific agents based on patient characteristics were conducted using Student *t* test and 1-way analysis of variance (ANOVA) with Scheffe correction. *P* values of $\leq$.05 were considered statistically significant. Statistical analyses were conducted using SPSS version 16.0 (SPSS, Chicago, IL).

RESULTS

During the study period (August 1, 2007, to September 30, 2008) there were 29,545 adult admissions to the University of Michigan Hospital. We identified 2189 patients (7.4% of all admissions) for whom intravenous hydralazine or labetalol was ordered as needed or "prn" (Figure). There were 7242 orders written for hydralazine and 5915 orders written for labetalol. There was wide variation in the ordered frequency of as-needed administration (Table).

There were 870 patients (39.7% of all patients) for whom medications were ordered but never administered (Figure). For the 1319 patients in whom drugs were administered, 412 patients (31.2%) received at least 1 dose of both hydralazine and labetalol, 581 patients (44.0%) received at least 1 dose of hydralazine only, and 326 patients (24.7%) received at least 1 dose of labetalol only. Thus, hydralazine was administered at least once to 993 patients (75.3%) and labetalol at least once to 738 patients (56.0%). For patients who received treatment, the average number of doses of hydralazine was 5.3±8.2 and the average number of administered doses of labetalol was 5.6±7.7.

Characteristics of the Patients

Patients who received both drugs had an average age of 60.5±16.5 years; hydralazine only, 62.3± 17.2 years; labetalol only, 58.3±17.5 years; and for those for whom orders were written but neither drug was administered, 54.4±18.8 years. Compared with patients who received both drugs, patients who received neither drug were significantly younger ($P<.001$ by ANOVA), while those who received hydralazine only were older ($P=.04$

by ANOVA). No other comparisons were statistically significantly different. Of the patients studied, 52.5% were men. There were no significant differences in which drug(s) were ordered or in the number of doses administered between men and women.

Of the 2189 patients in this study, only 64 (2.9%) had diseases for which aggressive BP-lowering therapy with intravenous agents could be indicated (described in the Methods section). Of these, 60 presented with subarachnoid hemorrhage, 2 with acute left ventricular dysfunction, 1 with hypertensive encephalopathy, and 1 with aortic dissection. A greater proportion of the patients with these conditions (46.9%) received labetalol plus hydralazine than patients without such diseases (18.0%). Hydralazine alone was administered to 14.1% of patients with concomitant diseases and to 26.9% of those without, and labetalol alone was administered to 12.5% of those with concomitant illnesses and to 15.0% of those without. For patients with these potential indications for intravenous therapy, 26.5% had drugs ordered but received neither agent, while 40.1% of patients without these conditions received neither drug.

LOS was longer in patients in whom intravenous antihypertensives were administered compared with those for whom the medications were ordered but not administered. LOS for patients for whom hydralazine was ordered and who received at least 1 dose was 12.0±15.9 days but only 7.1±9.0 days for those who did not receive a dose ($P<.001$). For patients for whom labetalol was ordered, patients receiving at least 1 dose had an LOS of 11.8±16.1 days vs 7.9±10.4 days for those who did not receive a dose ($P<.001$).

Table. Dosing Frequency Specified in Medication Orders

Dosing Frequency	Hydralazine, No. (%)	Labetalol, No. (%)
Single dose only	724 (10.0)	390 (6.6)
Every 5 min	4 (0.1)	612 (10.3)
Every 10 min	58 (0.8)	159 (2.8)
Every 15 min	69 (1.0)	165 (2.8)
Every 1 h	2332 (32.2)	2189 (37.0)
Every 2 h	1804 (24.9)	1433 (24.2)
Every 3 h	82 (1.1)	23 (0.4)
Every 4 h	1389 (19.2)	645 (10.9)
Every 6 h	780 (10.8)	299 (5.1)

DISCUSSION

Our findings document that treating hypertension in the in-patient setting with intravenous hydralazine and labetalol is a common practice. In order to provide as clear a picture as possible in this exploratory study, we limited ourselves to these two agents, and our data therefore likely represent an estimate of the minimal frequency of treatment of acute hypertension in the in-patient setting with intravenous drugs. There are many other treatments used for in-patient hypertension, including the oral administration of hydralazine and labetalol as well as other agents such as intravenous and oral β-blockers, calcium channel blockers, and oral clonidine, but since some of these agents are appropriately used for indications other than hypertension, we did not include them in the current study.

In our study, most patients who received treatment with intravenous labetalol or hydralazine for acutely elevated BP appeared not to have commonly accepted conditions warranting aggressive antihypertensive treatment, ie, hypertensive emergencies.[10] Only a small minority had such illnesses, suggesting that most of the treatment was administered for elevated BP alone, which is consistent with our personal observations in this hospital. Whether the experience in our tertiary care university hospital reflects practice in other settings, eg, community hospitals, is unknown.

Our data indicate that hydralazine is utilized somewhat more frequently than labetalol to treat acutely elevated BP and that a combination of both drugs was administered to almost a third of patients who received treatment. The only factor potentially related to the preference for one drug or the other was the slightly older age of patients who received hydralazine alone; sex did not seem to play a role. Patients who received both drugs more frequently had concomitant diseases for which antihypertensive treatment is indicated, and they had the longest LOS, suggesting that they may have been sicker than those who received hydralazine or labetalol only. Patients in whom drugs were ordered but not administered were significantly younger than those who received at least 1 dose of either or both drugs, which would be consistent with their being healthier. We do not have data bearing on the possibility that some orders were cancelled before drugs could be administered.

Drug treatment regimens were not ordered at intervals consistent with expert recommendations, which suggest that labetalol be dosed as 10- to 80-mg intravenous boluses every 10 minutes and hydralazine as 10- to 20-mg intravenous boluses every 4 to 6 hours.[11] Our data show that both drugs are ordered over a wide range of dosing intervals and that the distribution of dosing

intervals is similar for the 2 drugs, with the exception that labetalol is used more frequently at the shortest dosing interval (5 minutes). Failure to follow established recommendations for drug dosing may lead to hypotension if a relatively long-acting drug such as hydralazine is given too frequently and ineffective therapy if a short-acting agent such as labetalol is administered at widely spaced intervals.

Although physicians commonly treat acute hypertension in in-patients, we can find no consensus recommendation supporting the practice. The only statement we can find is contained in a paper that primarily addresses well-known issues related to treating hypertension in emergent or urgent settings, eg, acute stroke, aortic dissection, and acute coronary syndromes.[12] The authors comment on in-hospital hypertension and suggest that if "reactive hypertension," which they define as hypertension "secondary to pain, anxiety, respiratory distress, or urinary retention," can be excluded, patients with a prior diagnosis of hypertension should be restarted on their prehospital medications. The suggested boundaries of the BP ranges for moderate or severe elevations suggested by Herzog and colleagues[12] are not standard for the field based on Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) or other guidelines, nor are the classifications or recommendations referenced or otherwise supported. Likewise, no rationale for the particular drugs recommended is given, despite prior experience suggesting that there are no important differences between the pharmacologic classes of available agents used to lower BP in the acute setting.[2]

The assumption that treating acute hypertension is helpful can be questioned, and there are several settings in which hypertension control was formerly thought to be important where practice has changed. Treatment of asymptomatic hypertension in the emergency department was previously commonly undertaken but is not currently recommended.[13] Similarly, there has been considerable controversy over the years as to the appropriateness of treating elevated BP in acute ischemic stroke: recent guidelines of the American Stroke Association now recommend treatment only for the most dramatically elevated BPs (>220 mm Hg systolic or >120 mm Hg diastolic) and, even then, the strength of the evidence is only level V, ie, data from anecdotal case series.[14]

This study represents only a very limited initial analysis of how and why hypertension is managed in the in-patient setting. To better understand the practice it will be important to determine how other antihypertensive drugs are used, to understand how BP thresholds for drug administration are determined by clinicians and to extend observations beyond a single tertiary care hospital. We would also like to understand the impact of concomitant diagnoses and clinical scenarios and to determine whether treatment of elevated BP in in-patients is beneficial or harmful. Finally, there are costs associated with in-patient pharmacologic treatment, including the costs of drug acquisition and administration as well as a potential impact on hospital LOS and technology utilization.

In the absence of any outcome data supporting a benefit of treating acutely elevated BP in hospitalized patients, and in light of some suggestions that acutely lowering BP may be harmful,[3–5] it would seem reasonable to limit the use of parenteral therapy to situations in which acute target organ damage is suspected and not as a standing "prn" order targeted to elevated BP above a threshold level. While there is a paucity of data that even in those settings treatment is useful, there is a reasonable expectation of doing more good than harm. In the nonemergent in-patient setting, rather than "treating the numbers," the goal should be to facilitate long-term management of hypertension, which has been unequivocally shown to improve outcomes.

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