Management of Patients With Hypertensive Urgencies and Emergencies

A Systematic Review of the Literature

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BACKGROUND: Hypertensive urgencies and emergencies are common clinical occurrences in hypertensive patients. Treatment practices vary considerably because of the lack of evidence supporting the use of one therapeutic agent over another. This paper was designed to review the evidence for various pharmacotherapeutic regimens in the management of hypertensive urgencies and emergencies, in terms of the agents' abilities to reach predetermined "safe" goal blood pressures (BPs), and to prevent adverse events.

METHODS: MEDLINE was searched from 1966 to 2001, and the reference lists of all the articles were retrieved and searched for relevant references, and experts in the field were contacted to identify other relevant studies. The Cochrane Library was also searched. Studies that were eligible for inclusion in this review were systematic reviews of randomized control trials (RCTs) and individual RCTs, all-or-none studies, systematic reviews of cohort studies and individual cohort studies, and outcomes research. No language restrictions were used.

RESULTS: None of the trials included in this review identified an optimal rate of BP lowering in hypertensive urgencies and emergencies. The definitions of hypertensive emergencies and urgencies were not consistent, but emergencies always involved target end-organ damage, and urgencies were without such damage. Measures of outcome were not uniform between studies. The 4 hypertensive emergency and 15 hypertensive urgency studies represented 236 and 1,074 patients, respectively. The evidence indicated a nonsignificant trend toward increased efficacy with urapidil compared to nitroprusside for hypertensive emergencies (number needed to treat [NNT] for urapidil to achieve target BP, 12; 95% confidence interval [95% CI], number of patients needed to harm [NNH], 5 to NNT, 40 compared to nitroprusside). Several medications were efficacious in treating hypertensive urgencies, including: nicardipine (NNT for nicardipine compared to placebo, 2 in one study [95% CI, 1 to 5] and 1 in another [95% CI, 1 to 1]); laclidipine (NNT, 2; 95% CI, 1 to 8 for laclidipine vs nifedipine) or urapidil (NNT for urapidil compared to enalaprilat and nifedipine, 4; 95% CI, 3 to 6); and nitroprusside and fenoldopam (all patients reached target BP in 2 studies). The studies reported 2 cases of cerebral ischemia secondary to nifedipine.

CONCLUSIONS: Many effective agents exist for the treatment of hypertensive crises. Because of the lack of large randomized controlled trials, many questions remain unanswered, such as follow-up times and whether any of the studied agents have mortality benefit.

KEY WORDS: hypertensive urgency; hypertensive emergency; hypertensive crisis.
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Hypertensive urgencies and emergencies are common clinical occurrences that may account for as many as 27.5% of all medical emergencies presenting to the emergency department and 3% of all emergency room visits, and that may affect as many as 1% of hypertensive patients. However, clinical treatment practices for the management of hypertensive urgencies and emergencies vary considerably. This practice variability is in part because of the lack of evidence supporting the use of one therapeutic agent over another. This paper was designed to review the evidence for various pharmacotherapeutic regimens in the management of hypertensive urgencies and emergencies in terms of the agents' ability to reach a predetermined "safe" target blood pressure (BP) and to prevent adverse events.

For this paper, we used the following definitions for hypertensive urgencies and emergencies, which were taken from the literature: in a hypertensive emergency, a patient has evidence of target end-organ damage, such as encephalopathy, unstable angina, stroke, or a dissecting aortic aneurysm. The absolute level of BP in this situation is not as important as the evidence of end-organ damage. In hypertensive urgencies, the patient has elevated BP but has no evidence of end-organ damage.

METHODS

Search Strategy

We searched MEDLINE from 1966 to 2001 using the terms hypertensive urgency, hypertensive emergency, hypertensive crisis, uncontrolled hypertension, refractory
hypertension, poorly responsive hypertension, poorly responsive blood pressure, and malignant hypertension. We also used search terms for finding systematic reviews.\textsuperscript{5} We then retrieved the references of all the articles and searched the bibliographies for additional relevant references. Experts in the field were contacted to identify any relevant studies. We also searched the Cochrane Library using the terms hypertension and malignant hypertension. Studies that were eligible for inclusion in this review were systematic reviews of randomized control trials (RCTs) and individual RCTs, all-or-none studies, systematic reviews of cohort studies and individual cohort studies, and outcomes research, i.e., Level 1 or 2 evidence. We did not include any language restrictions in the literature search. Our study included all classes of antihypertensive agents. The agents could have been given via sublingual (SL), oral (PO), or parenteral (IV) routes, depending on the agent and the setting.

The articles were appraised by 2 independent reviewers who assessed their level of evidence on the basis of the definitions that can be found in Table 1. Levels of evidence are useful in assessing the validity of evidence and in interpreting evidence. They have been designed to identify the specific methods that maximize the validity of a study’s conclusions and structure them into a hierarchy of study types with the most valid at the forefront.\textsuperscript{6} Only those articles with Level 1 or 2 evidence were included in this review. Number needed to treat (NNT) and relative risk (RR) calculations were performed using the Mount Sinai Hospital Center for Evidence Based Medicine statistics calculator\textsuperscript{7} and were included for comparative purposes. The NNT calculations were given, when possible, for the most effective agent in trials comparing more than 1 antihypertensive. The RR calculations were also performed, when possible, to give an estimate of the likelihood of the less-effective agent reaching the target BP.

### Study Participants

Study participants were over the age of 18 years and had had a hypertensive emergency or urgency at the time of their enrollment in the study. Exclusion criteria were varied and included the very elderly (>80 years old),\textsuperscript{8,9} pregnancy and lactation,\textsuperscript{8-19} history of organ transplantation,\textsuperscript{8,17} immunosuppression,\textsuperscript{17-19} acute\textsuperscript{8,9,17,18} or chronic renal failure,\textsuperscript{8,11,12,17,18,20} dialysis,\textsuperscript{17-19} valvular heart disease,\textsuperscript{11,12,14,21} recent stroke,\textsuperscript{6} acute myocardial infarction,\textsuperscript{9,11,12,14-16,21} coronary bypass surgery or congestive heart failure,\textsuperscript{11,12} bilateral stenosis\textsuperscript{9} or arrhythmia,\textsuperscript{15-20} or a known secondary cause of hypertension such as pheochromocytoma.\textsuperscript{8,17-19} Other exclusion criteria included hypothyroidism,\textsuperscript{19} hepatic\textsuperscript{14,15,17-19} or hematological disease,\textsuperscript{14,17,18} asthma or chronic obstructive pulmonary disease,\textsuperscript{16} alcohol intoxication,\textsuperscript{12} parenteral analgesia,\textsuperscript{17,18} dopamine antagonists\textsuperscript{17-19} or “considerable pain.”\textsuperscript{13} Patients with signs of end-organ involvement were excluded in the hypertensive urgency studies. Signs of end-organ involvement (acute myocardial infarction, aortic dissection, and focal neurological deficits) aside from hypertensive changes in the retina were exclusion criteria in 1 study of hypertensive emergencies.\textsuperscript{10}

### RESULTS

Six hundred hypertensive urgency or hypertensive emergency abstracts were identified in the literature. Most of these studies were excluded because they were non-human studies, did not involve patients with high enough BP to qualify as an urgency or an emergency, were safety/tolerability studies, or were case-series or case reports. We were left with 39 studies after excluding all of the above. Ten studies were then excluded because they did not include a target BP and were therefore of limited usefulness to clinicians and could not be compared to other agents in terms of NNT or RR. Other studies were excluded because they were methodologically flawed in their randomization (5 studies) or because the target BP was arbitrarily described as an appropriate target BP according to the treating physician (1 study). Methodologically flawed RCTs were excluded because they were of a lower quality and level of evidence compared to some of the well-designed cohort studies that we evaluated. Other reasons for exclusion were that the study involved nonpharmacological interventions (e.g., coffee and cigarette smoking or concurrent hemodialysis)\textsuperscript{2} or that the study was a follow-up of patients who had already been treated for a hypertensive emergency or urgency\textsuperscript{1} or who had had a run-in period with other drugs (1 study), making the interpretation of the results very difficult in terms of the drug of interest. Nineteen trials met the criteria for Level 1 or 2 evidence. The 4 hypertensive emergency and 15 hypertensive urgency studies represented 236 and 1,074 patients, respectively.

Eight of the 19 trials included in this review were open label or did not mention if the trial was