Phenylpropanolamine and Other Over-the-Counter Vasoactive Compounds

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SUMMARY Phenylpropanolamine is a sympathomimetic amine that shares structural similarities with amphetamine and ephedrine. It increases blood pressure primarily by increasing peripheral vascular resistance. This effect is the result of α-adrenergic agonist activity largely from both direct stimulation of adrenergic receptors and release of neuronal norepinephrine. As such, it has the potential to interact with other drugs to produce toxic reactions, especially in treated hypertensive patients. Complications have occurred with single oral doses that suggest some normal subjects may be more sensitive to the drug than others. The incidence of serious complications in the general population is small but could be much higher in susceptible individuals (e.g., cardiomyopathic and hypertensive patients). The availability of high-dose phenylpropanolamine-containing preparations without medical supervision is potentially dangerous, and certain restrictions should be imposed on such preparations. (Hypertension 11 [Suppl II]: II-7-II-10, 1988)

KEY WORDS • hypertension • phenylpropanolamine • over-the-counter drugs • vasoactive compounds

PHENYLPROPANOLAMINE (PPA) is a sympathomimetic amine that is widely used as a constituent of over-the-counter nasal decongestants and anorectic medications. However, its sustained therapeutic benefit as an appetite suppressant and its value in nasal decongestants has been questioned. Recently, serious complications have been attributed to ingestion of PPA-containing drugs. These complications include severe hypertension,1-3 headaches,4,5 neuropsychiatric symptoms,6 cardiac arrhythmias,7 myocardial injury,8 stroke,9 and death in previously healthy individuals.10 This article has a fivefold purpose: 1) to give a brief survey of the biochemistry and clinical pharmacology of PPA, 2) to review the reported clinical responses to PPA, 3) to assess the prevalence and extent of complications attributed to PPA, 4) to determine the population at risk of developing complications to PPA, and 5) to offer some recommendations based on experience gathered from a review of the literature on the subject.

Chemistry and Structure-Activity Relationship of Phenylpropanolamine

β-Phenylethylamine is considered the parent compound of the sympathomimetic amines. It consists of a benzene ring and an ethylamine side chain. Substitutions on the aromatic ring, the α- and β-carbon, and the terminal amino group yield various compounds with sympathomimetic activity. The greatest sympathomimetic activity occurs when two carbon atoms separate the benzene ring from the amino group.

PPA shares structural similarities with amphetamine and ephedrine (Figure 1). Comparison of the structural similarity between PPA and metaraminol is especially helpful in understanding their pressor actions. In general, substitution at the amino terminal group increases β-receptor activity, and the less the substitution, the greater is the selectivity for α-receptor activity, although N-methylation increases the potency of primary amines. Phenylethylamine has little β-receptor activity because, unlike ephedrine, it lacks a methyl substitution at the amino terminal end. Maximal α- and β-receptor activity depends on the presence of hydroxyl groups in the third and fourth positions of the aromatic nucleus. Absence of aromatic substitutions results in reduction of overall potency and some loss of direct peripheral sympathomimetic activity. In addition, compounds devoid of polar hydroxyl groups cross the blood-brain barrier more readily and therefore have more central activity. Thus, amphetamine, ephedrine, and PPA exhibit considerable central nervous system activity. This also explains why PPA is less potent as an α- and β-agonist than is metaraminol. Absence of the 3-OH group also increases the oral effectiveness and the duration of action of such compounds.

Substitution on the α-carbon atom blocks oxidation
by monoamine oxidase (MAO), greatly prolonging the duration of action of these compounds. Protection from rapid degradation by MAO allows these compounds to persist in nerve terminals and release norepinephrine from storage sites.

Substitution on the β-carbon atom generally decreases central stimulant action largely because of the lower lipid solubility. However, such substitution greatly enhances agonistic activity both at α- and β-receptors.

In summary, PPA 1) has more marked α- than β-activity because of the absence of an alkyl substituent at the terminal amino group and because of substitution at the β-carbon atom; 2) has considerable central nervous system activity that results from the absence of aromatic substitutions but is less potent than amphetamine because of substitution at the β-carbon atom, which tends to lower lipid solubility; 3) is likely to persist in nerve terminals and release norepinephrine from storage sites. This property results from substitution on the α-carbon atom, which blocks degradation by intraneuronal MAO; 4) is orally active with prolonged duration of action by virtue of the absence of the 3-OH group on the benzene ring, which blocks the MAO enzyme in liver and intestine.

The effects of PPA are largely the result of α-adrenergic agonist activity resulting from both direct stimulation of adrenergic receptors and release of norepinephrine from neuronal storage sites. The hypertension induced by PPA is presumably due to those effects. The increase in blood pressure is characterized by increases in cardiac output, peripheral vascular resistance, stroke volume, ejection fraction, and decreases in heart rate (Table 1). Because of its vasoconstrictor activity, the administration of PPA to patients with compromised myocardial function could result in deterioration of cardiac performance.

### Proprietary Preparations Containing Phenylpropanolamine and Other Sympathomimetic Agents

PPA is an ingredient in more than 70 over-the-counter preparations. Table 2 shows the products containing 25 mg or more per unit dose of PPA. Eleven have PPA as the only ingredient. These are usually sold as decongestants or as appetite suppressants. All others are combined with an antihistamine (chlorpheniramine), an antitussive (dextromethorphan), an expectorant (guaifenesin), or an analgesic (acetaminophen). These are usually sold as decongestants and cold remedies. The dose varies widely from preparation to preparation. It is as little as 3.125 mg in children’s cold tablets and as much as 75 mg in adult diet pills. The highest recommended adult dosage of PPA for use as anorectics is 75 mg/day, and for use as decongestants and cough remedies, 150 mg/day is recommended.

PPA is also an ingredient of pills made to look like amphetamine-containing and other prescription drugs. These preparations are called “look-alike” pills and are sold in the streets as “uppers” and sold legally in “pick-me-up” shops and mail-order shops. They contain as much as 50 mg PPA, 25 mg ephedrine, and 200 mg caffeine. Their street names include “pink ladies” (pink, heart-shaped tablets), “black beauties” (black capsules with numbers or letters printed on them), and “speckled pups” (white tablets with colored speckled markings, often oblong and scored).

Sixty-five other over-the-counter drugs contain various concentrations of sympathomimetic agents other than PPA. These include phenylephrine in 9, pseudoephedrine in 41, oxymetazoline HCl in 10, and ephedrine in 5. At the latest count, there are at least 133 over-the-counter drugs with sympathomimetic agents as one of the active ingredients.

### Clinical Responses to Phenylpropanolamine

The numbers of patients exposed to significant doses of the drug are unknown, and the reporting scheme may only gather details of a proportion of those patients who develop significant signs and symptoms. It is, therefore, not possible to estimate the frequency of the occurrence of complications caused by the drug in the general population. Clinically significant signs and symptoms from limited studies and case reports in the literature form the basis of this assessment.
Hypertension

There is little information in the literature about the incidence and severity of hypertensive reactions in the hypertensive population. Prospective studies in healthy normotensive subjects revealed dose-related increases in blood pressure with single oral doses of PPA (immediate-release formulation) Horowitz et al. demonstrated in a group of young, healthy normotensive subjects significant and potentially dangerous rises in blood pressure after ingestion of a single capsule of a preparation containing 85 mg PPA. In this study, 12 of 37 subjects had a supine diastolic blood pressure rise to 190/142 mm Hg. In a more recent study, 12 of 37 subjects had a supine diastolic blood pressure rise to 100 mm Hg or more, and one had a blood pressure rise to 190/142 mm Hg. In a more recent study, Pentel and co-workers demonstrated that single oral doses of 37.5 and 75 mg PPA (immediate-release formulation) produced dose-related increases in both systolic and diastolic blood pressures. However, Goodman and co-workers found that a slow-release preparation (75 mg), given either acutely or chronically, had no effect on 24-hour ambulatory blood pressure in 18 normotensive males.

In other studies, similar doses of PPA in slow-release preparations produced only modest or no increases in blood pressure. However, in some patients, significant increases in blood pressure have been observed with slow-release formulations, indicating that some subjects may be more sensitive to PPA than others.

Reports of serious complications (i.e., stroke, seizures, and cerebral hemorrhage) resulting from significant hypertension have generally been related to intake of PPA-containing drugs in more than the recommended doses or from self-medication with look-alike or fake amphetamine pills. Because these pills are not as potent as amphetamines, the user is more likely to take several at a time to obtain an effect equivalent to taking amphetamines. Because PPA and ephedrine have much more pronounced peripheral effects than do amphetamines, the hypertensive reactions from these stimulants are greater. Hypertensive crises and intracerebral hemorrhages culminating in death have been reported with use of these drugs.

In addition, concomitant medications may sensitize the patient to the hypertensive effects of PPA. Interactions between PPA and MAO inhibitors, indomethacin, and antihypertensive drugs (α-methylldopa and oxprenanolol) have been described. MAO inhibitors potentiate the pressor effects of PPA by raising the concentration of catecholamines at nerve endings and making them available for release. By the same token, tyramine in foodstuff can act synergistically with PPA to enhance release of norepinephrine at nerve endings. Indomethacin, an inhibitor of prostaglandin synthesis,
potentiates the direct and indirect effects of PPA. The mechanism by which this interaction occurs is unclear. The widespread use of nonsteroidal anti-inflammatory drugs makes the use of PPA a greater risk to the public than is generally recognized.

The mechanism by which PPA and methyldopa interact to produce a hypertensive crisis is not well understood. It is possible that PPA and α-methylnorepinephrine, a metabolite of methyldopa, act synergistically at vascular sites to cause severe peripheral vasoconstriction. Alternatively, patients receiving α-methyldopa could be supersensitive to the direct α-adrenergic agonist activity of PPA.

Cardiac Complications

In addition to hypertensive effects, arrhythmias have been reported by Weesner et al. These authors postulate that the hypertension produced by PPA results in reflex bradycardia that may allow the ectopic pacemaker to assume control of the ventricles. Clinical evidence of acute myocardial injury after acute ingestion of PPA has also been substantiated.

Neurological Complications

Headaches, neuropsychiatric symptoms, and generalized convulsive seizures are common toxic reactions with large doses of PPA. Amphetamine-like reactions have also been described. These effects range from stimulation of the medullary respiratory center to tremor, restlessness, increased motor activity, agitation, and hallucinations.

From these reports, it can be concluded that the ability of PPA to induce toxic reactions depends, to a large extent, on the dose and rate of absorption. Those preparations in which PPA is present in the immediate-release rather than in the slow-release form seem particularly apt to produce severe hypertensive reactions. Other factors such as concomitant medications may sensitize patients to the effects of PPA. In addition, idiosyncratic reactions could have played a role in some reports. In general, toxic reactions attributed to slow-release PPA-containing preparations have been related to intake of more than the recommended dosages.

Conclusions

PPA is a potent sympathomimetic, and its hypertensive effect is dose related. Hypertensive episodes are more likely to occur with preparations containing PPA in the immediate-release than in the slow-release form. Most reported reactions result from either self-medication or intake of more than the recommended dosage (or both). However, reactions from single oral doses (50–75 mg) have been reported, and adverse interactions with commonly used drugs have been demonstrated.

Effects of PPA are the result of α-adrenergic agonist activity largely from both direct stimulation of adrenergic receptors and release of neuronal norepinephrine. As such, it has the potential to interact with other drugs to produce toxic reactions, especially in treated hypertensive patients. The occurrence of complications with single oral doses suggests that some normal subjects may be more sensitive to the drug than others. Although the incidence of serious complications in the general population is probably small, the availability of high-dose PPA-containing preparations without medical supervision is potentially dangerous, and certain restrictions should be imposed on such preparations.

References

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Hypertension. 1988;11:II7
doi: 10.1161/01.HYP.11.3_Pt_2.II7

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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