

Review Article

Experience (Mostly Negative) with the Use of Sympathomimetic Agents for Weight Loss

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Sympathomimetic agents have a poor history of long-term success in the treatment of obesity. From earlier experiences with amphetamine and its analogs, to more recent drugs with direct effects on adrenergic receptors or indirect effects from release of catecholamines or inhibition of reuptake, cardiovascular toxicity (strokes and cardiac arrhythmias) has been the major concern. These concerns also extended to food supplements containing ephedra alkaloids and may require consideration for current supplements containing the sympathomimetic drug, synephrine.

Sibutramine is the most recent drug with sympathomimetic activity that has been recognized by regulatory agencies as having cardiovascular adverse effects that may outweigh its potential value as a weightloss drug. Sibutramine is marketed in Europe under several trade names, including Reductil, Reduxade, Ectiva, Sibutral, Zelium, and others. Meridia is the only brand name in the United States. The European Medicines Agency took definitive action on January 21, 2010 in advising against the continued prescribing of the drug, and Abbott Laboratories suspended sales of the drug in Europe [1]. This action was prompted by a preliminary evaluation of results from the Sibutramine Cardiovascular OUTcome (SCOUT) trial reported by the United States FDA [2]. The FDA has not imposed a ban on the drug but has obtained a change in the boxed warning label to contraindicate its use in patients with a history of cardiovascular disease and in all individuals over 65 years of age (updated warning, April 15, 2010). These regulatory actions were prompted by an early review of the SCOUT trial [3] that revealed an incidence of cardiovascular events of 11.4% in patients receiving sibutramine compared to 10% in those receiving placebo. This was an unexpected finding; the hypothesis in the design of the study was that an anticipated weight loss from the use of sibutramine would be associated with a reduction in the incidence of cardiovascular events when

compared to that observed in patients receiving the placebo treatment [3].

Sibutramine was not developed as a sympathomimetic drug. In early studies, it was first evaluated for its potential as an antidepressant medication, and its behavioral effects were apparently explained by its inhibition of both 5-hydroxytryptamine (5-HT) and norepinephrine reuptake in the central nervous system (CNS) [4, 5]. The inhibition of monoamine uptake is produced almost completely by two metabolites of sibutramine [5]. The hypophagic effect of sibutramine was recognized later, and this became the focus of its development as an antiobesity drug [6–8]. Its sympathomimetic effects (an increase in heart rate and blood pressure), which are of concern in relation to the observed increase in adverse cardiovascular events, would appear to be primarily related to a peripheral inhibition of norepinephrine reuptake and interrelationships with sympathetic outflow from the CNS [9, 10]. The increases in heart rate and blood pressure would be expected to follow from inhibition of norepinephrine reuptake by sibutramine (mostly its metabolites) at sympathetic nerve endings in the heart and blood vessels. This effect would be magnified during physical activity or other conditions of stress that would increase sympathetic nerve activity and norepinephrine overflow in the periphery. These increases

in heart rate and blood pressure are seen, despite the fact that sibutramine is known to blunt the intensity of central sympathetic outflow by virtue of α_2 -adrenergic suppression of sympathetic activity in the CNS. The locus of this action is considered to include α_2 -adrenergic receptors in the lower portion of the brain stem (medulla oblongata) [11]. This is also the presumed site of action of the antihypertensive drug, clonidine. The extent to which sympathetic outflow is decreased by this central inhibitory effect of overflow norepinephrine may be limited, because sibutramine has been observed to rapidly (within days) desensitize central α_2 -adrenergic receptors in animal studies [12].

Amphetamines, phentermine, and phenyl-propanolamine (PPA) are sympathomimetic amines that were once widely used for the treatment of obesity because of their anorexic effects [13, 14]. They are all contraindicated for this use at this time because of their adverse cardiovascular and/or behavioral profiles. They are primarily indirect acting amines, that is, they release norepinephrine from sympathetic nerve endings. These amines all have an α -methyl substitution, which results in inhibition of monoamine oxidase and an intensification and prolongation of their pharmacological effects. In addition, the *dextro* isomer of amphetamine, dexamphetamine, is a potent inhibitor of norepinephrine reuptake, which may be the basis for its greater potency over the *levo* isomer [13]. The unregulated sale of supplements containing ephedra alkaloids is probably the most recent example of the discontinued use of a group of sympathomimetic entities for weight loss. These supplements were banned by the FDA in 2004 because of their unreasonable risks of cardiovascular toxicity. The complete ban on ephedra sales was challenged in 2005; that challenge was overturned on appeal by the FDA, with confirmation of the ban in 2006. The United States Supreme Court declined to review a further industry appeal in 2007. (I have commented previously on the cardiovascular risks of ephedra alkaloids [15].)

As one of several consultants to the FDA before the imposition of the ephedra ban [16], I conducted an evaluation of the pharmacology and inherent safety concerns of ephedra alkaloids. The principal focus in that analysis concerned ephedrine. Although the natural herb, *Ephedra sinica* (Ma Huang), contains three sympathomimetic agents in addition to ephedrine (pseudoephedrine, methylephedrine, and phenylpropanolamine), ephedrine is the most potent and is typically present in the highest concentration among the four alkaloids [17]. The sympathomimetic impact of ephedrine results from a combination of multiple actions. Ephedrine is classified as both a direct and indirect acting amine. Its indirect effects result primarily from the fact that it causes a displacement release of norepinephrine from sympathetic nerve endings. In addition to releasing norepinephrine, ephedrine blocks the reuptake of norepinephrine into sympathetic nerve terminals. Ephedrine is also an inhibitor of the degradation of norepinephrine by monoamine oxidase. Thus, by three mechanisms, ephedrine magnifies the intensity and duration of action of norepinephrine that is released [13, 14, 18]. Obviously, this entire process is further amplified during periods of physical

exercise, where sympathetic nerve activity is increased. In addition to indirect effects of ephedrine, it also has direct vasoconstrictor (α_1 -adrenergic), cardiac acceleration and increased contractility (β_1 -adrenergic), and bronchodilator (β_2 -adrenergic) effects. This triad of effects is similar to that of epinephrine. The direct effects of ephedrine summate with its indirect effects to produce its total cardiovascular impact.

A major negative impact of ephedrine upon the heart is its ability to induce cardiac arrhythmias. The primary mechanism involved in this risk is the fact that ephedrine and all sympathomimetic drugs that activate β_1 -adrenergic receptors (either directly or through release, inhibition of reuptake, or inhibition of metabolism of norepinephrine) shorten the refractory period of the conducting system of the heart and cardiac muscle [11]. This is particularly problematic in an individual who is exercising, because the increased sympathetic outflow with exercise augments the release of norepinephrine, which itself has β_1 -adrenergic activity. This adds to the shortening of refractoriness of cardiac cells. A shortening of the refractory period of myocardial cells is an essential element in the induction of a re-entrant arrhythmia, that is, an impulse may now encounter receptive cells, cells that would ordinarily be refractory and would not allow for a premature activation. That premature activation can permit an abnormal route of electrical excitation, that is, an arrhythmia [19]. In addition, myocardial ischemia caused by exercise and/or exacerbated by the presence of coronary artery obstruction also results in a shortening of the refractory period of myocardial cells [19, 20]. Since the presence of coronary artery disease may be unrecognized in many individuals during routine activities, the summation of drug and stress effects on the electrophysiology of the heart requires consideration. Recent data presented by the American Heart Association shows that the incidence of cardiovascular disease is 39.6 percent in the age group 40 to 59 years (identical for men and women) and 73.6 percent and 73.1 percent in the age group 60 to 79 years for men and women, respectively [21].

In addition to the risks of stroke associated with blood pressure elevations produced by sympathomimetic drugs, increases in blood pressure may also contribute an arrhythmogenic potential. With increases in blood pressure, compensatory baroreceptor-mediated predominance of the parasympathetic nervous system does result in a slowing of heart rate in comparison to the effect that would take place as a result of β_1 -adrenergic activation alone. Although this may reduce the extent of blood pressure elevation, it does not reduce the arrhythmogenic potential of the electrophysiological processes discussed above. In fact, the participation of the parasympathetic nervous system to slow heart rate does so by release of its mediator, acetylcholine. Acetylcholine also shortens the refractory period of atrial tissues, which may be causally related to the induction of atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia [11]. Thus, direct sympathomimetic stimulation of β_1 -adrenergic receptors, indirect effects through released norepinephrine, ischemia, and compensatory acetylcholine release, may each be primary or may summate to induce cardiac arrhythmias.

As a result of the loss of availability of ephedra-containing products, the sympathomimetic amine, synephrine, appears to have become an important focus of the food supplement industry. Synephrine is chemically related to the well-known vasopressor drug, phenylephrine; phenylephrine is the *meta*-hydroxy-phenyl isomer of synephrine. As with phenylephrine, synephrine increases blood pressure through its α_1 -adrenergic-mediated vasoconstrictor effect [13]. There are a number of supplements currently on the market that identify synephrine as a major ingredient of the product. Information about these products is readily available through searches for synephrine. Various claims are made as to the value of this constituent for weight loss and development of physical fitness. Several of these commercial products contain a fairly well-characterized extract of *Citrus aurantium* (bitter orange), which is called "ADVANTRA Z". ADVANTRA Z is supplied by Nutratech, Inc. [22]. The descriptions of patents for ADVANTRA Z indicate that, in addition to synephrine, it contains three other orally active sympathomimetic agents, N-methyltyramine, hordenine, and octopamine [13]. The Nutratech website suggests a daily intake of 100 to 120 mg of synephrine, in two to three divided servings.

The potential cardiovascular effects of the doses of synephrine present in ADVANTRA Z can be placed in perspective because synephrine is the active ingredient in the orally active vasopressor drug, oxedrine tartrate. A common trade name for this preparation in Europe is Sympatol [23]. Oxedrine tartrate is not marketed in the United States. Sympatol carries the clinical indication for the treatment of hypotension, that is, to *raise* blood pressure, with oral doses of 100 to 150 mg, up to three times a day. To compare doses of synephrine in ADVANTRA Z with clinical doses of Sympatol, it is necessary to correct for the fact that Sympatol is the racemic mixture of synephrine (the *l*-isomer has the predominant sympathomimetic activity) and that it is the tartrate salt. (The *l*-isomer of synephrine is the form in citrus extracts [24, 25].) Therefore, the molecular weight of synephrine tartrate is 484.5. Of this, the *l*-synephrine content is 167.2 or 34.5% of the dose.

Thus, the single oral dose range of 100 to 150 mg of Sympatol supplies 34.5 to 51.8 mg of *l*-synephrine. If 3 doses are given per day, the total daily dose would be 103.5 to 155.4 mg of synephrine. This overlaps the suggested intake for ADVANTRA Z of 100 to 120 mg of synephrine per day. As discussed above, in addition to the danger of stroke associated with drug-induced increases in blood pressure, compensatory responses to these increases, mediated through the parasympathetic nervous system, may be arrhythmogenic. Also, these concerns would be expected to be enhanced in conjunction with physical effort. The National Center for Complementary and Alternative Medicine, National Institutes of Health, has noted the potential risks for cardiovascular toxicity from consumption of extracts of *Citrus aurantium* [26].

In summary, sympathomimetic agents do not have a successful record for the treatment of weight loss. They apparently possess an unreasonable cardiovascular toxic potential that emerges when the drugs are applied to a

broad spectrum of the population, many of whom may have unrecognized risk factors.

Disclosure

The author was compensated as a consultant to the US Food Administration for evaluation of sympathomimetic agents in food supplements.

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