

Phentermine and other monoamine-oxidase inhibitors may increase plasma serotonin when given with fenfluramines

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Phentermine has been used in the USA to treat obesity since at least 1961 and was widely used after 1992 in combination with fenfluramine. A study in 1997 suggested that this combination could be associated with heart-valve disease similar to that seen in the carcinoid syndrome or in patients who had taken ergotamine, as well as with pulmonary hypertension, previously described.¹ It was suggested that these findings, were due to an increase in circulating serotonin. Subsequently, the US Food and Drug Administration found heart-valve lesions among patients taking a fenfluramine without phentermine.

Given the paucity of data on phentermine's actions, we determined whether phentermine could modify the metabolism of other monoamines besides the norepinephrine released from sympathetic neurons. In rats, phentermine, like *d*-amphetamine, releases dopamine into brain synapses.² We tested the ability of a low dose (15 mg by mouth) to affect plasma dopamine in human beings. Nine young, non-obese male volunteers gave blood just before, and 1, 2, or 4 h after receiving the drug. Plasma dopamine concentrations, assayed by radioimmunoassay³, rose with phentermine ($p < 0.05$; ANOVA; Wilcoxon's test); however a greater increase was noted in serotonin levels within the blood platelets as assayed by ELISA and confirmed by high performance liquid chromatography ($r = 0.496$; $p < 0.001$). The increase in platelet serotonin could reflect increased release of serotonin from enterochromaffin cells, or inhibition of its metabolism by monoamine oxidase (MAO). That the increase resulted from MAO inhibition and not from increased serotonin release was shown by the finding that plasma serotonin concentration fell slightly.

That phentermine inhibits the MAO which catabolises serotonin was well known in the early 1970s,⁴ but apparently this information never made its way onto the drug's label. There is evidence that free plasma serotonin can damage vascular tissue⁵ and that its concentration is normally kept low by the action of the two high-capacity systems that remove it from the circulation—uptake into platelets and MAO. If the fenfluramine and phentermine regimen did produce pulmonary hypertension and cardiac valve lesions then they might have been obviated had the phentermine label within the US mentioned that the drug is an MAO inhibitor. Such a mention would also warn physicians against combining phentermine with fluoxetine, fenfluramine, or other SSRIs.

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