

# Fenfluramine Anorexients and Anesthesia

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## Citation

D Oeser. *Fenfluramine Anorexients and Anesthesia*. The Internet Journal of Advanced Nursing Practice. 1996 Volume 1 Number 1.

## Abstract

Nearly one out of every three adults in the United States is obese and the prevalence is increasing according to a 1995 report by the Institute of Medicine (1). Obesity, in combination with other risk factors, is responsible for the deaths of an estimated 300,000 Americans each year (2). Similar trends have been noted worldwide (3).

The mainstay for weight reduction is diet modification and exercise. Appetite suppressant drugs (anorexients) are considered adjuncts to diet and behavior modification and exercise, and have traditionally been indicated only for short term use (4). Recently however, controlled clinical trials have demonstrated longer term weight reduction when anorexient medications are used in conjunction with diet modification and exercise (5,6). News of this data, along with the marketing of the newest prescription anorexient dexfenfluramine (Redux® - Wyeth-Ayerst Laboratories), will undoubtedly cause a resurgence in the use of diet pills. Anesthesiology practitioners are likely to encounter a increasing number of patients who are taking anorexients and therefore need to be knowledgeable about the potential risks of anesthesia in patients taking these agents.

Fenfluramine (Pondimin®- AH Robins) and dexfenfluramine are anorexients that induce the release and inhibit the reuptake of serotonin (7,8). Elevated brain serotonin levels are associated with early satiety and appetite suppression. Fenfluramine, is a racemate of the dextro- and levo-rotatory isomers of fenfluramine and is a commonly prescribed anorexient. According to the manufacturer's prescribing information the drug is contraindicated in patients undergoing general anesthesia because of a possible interaction with halogenated anesthetics. Because the half-life is 20 hours, the drug should be discontinued at least 5 days prior to the administration of anesthesia. Dexfenfluramine, the biologically active dextro-rotatory stereoisomer of fenfluramine, has been available in Europe

for many years and was recently approved by the FDA in the United States (9). Unlike fenfluramine however, dexfenfluramine is not contraindicated in patients undergoing anesthesia.

The manufacturer's prescribing information advises that fenfluramine is contraindicated in patients undergoing general anesthesia because of a single case report of a fatal cardiac arrest following the induction of anesthesia with halothane in a patient who had been taking fenfluramine prior to surgery (10)(12). It was postulated that fenfluramine may have had a catecholamine-depleting effect that may have led to cardiovascular collapse upon exposure to halothane. In vivo experiments in rabbits receiving fenfluramine and halothane seemed to be consistent with this hypothesis (10). However, neither the clinical information presented in the case report nor the design of the drug interaction experiment were adequate to answer the question of whether or not a interaction exists (11). Nevertheless, the manufacturer recommends that potent anesthetic agents be administered with caution to patients taking fenfluramine and if general anesthesia cannot be avoided, full cardiac monitoring and facilities for instant resuscitation measures are a minimum necessity (12). More recently, a letter from the Texas Society of Anesthesiologists concerning the administration of anesthesia to patients taking fenfluramine warned of the potential medical-legal risks (13).

Since the initial case report by Bennett and Eltringham however, there have been no further reports of adverse events related to a anesthetic interaction with either fenfluramine or dexfenfluramine and unfortunately no definitive drug interaction studies have been conducted. Information obtained under the Freedom of Information Act from the U.S. Food and Drug Administration also failed to reveal any additional

reports of adverse events related to the use of fenfluramine and anesthesia. Thus the question remains: Is there a drug interaction between fenfluramine and anesthetic agents?

The fact that the patient described by the Bennett and Eltringham was noted to have become “pulseless, cyanosed, and developed signs of acute pulmonary edema” suggests that, in addition to cardiogenic shock, other etiologies may have been responsible. Could the development of acute pulmonary hypertension leading to overt right-sided heart failure and cardiogenic shock have been responsible for the fatal outcome? Several lines of evidence including the role of serotonin in the association between anorexiant-induced pulmonary hypertension along with data on the effects of halogenated anesthetics on the pulmonary handling of serotonin suggest the possibility of a interaction.

Appetite suppressant drugs have long been implicated in the development of pulmonary hypertension since the 1960s, during an outbreak of pulmonary hypertension in Western Europe related to the use of aminorex fumarate (14,15). Both fenfluramine and dexfenfluramine have been implicated in case reports and epidemiologic studies (16,17,18,19,20). High doses of fenfluramine have induced acute fatal pulmonary hypertension in rats (21). Dexfenfluramine has also been implicated in several case reports of pulmonary hypertension (22,23). The mechanism involved in the development of pulmonary hypertension is not entirely clear but recent evidence strongly suggests a role for serotonin (24).

Markedly increased plasma serotonin concentrations were reported in a series of patients with pulmonary hypertension including three patients who were taking fenfluramine (24). The data suggested that the increased plasma serotonin was due to abnormalities in the handling of serotonin by platelets. Experimental evidence has shown that fenfluramines inhibit the uptake, promote the release, and interfere with the storage of serotonin in platelets (25,26). Furthermore, fenfluramine treatment has been associated with decreased platelet serotonin concentrations in boys with attention deficit disorder (27). Therefore, in addition to elevating brain serotonin levels, fenfluramines appear to be

capable of increasing the circulating plasma concentrations of serotonin by decreasing platelet uptake and interfering with platelet storage.

Serotonin is a potent constrictor of the pulmonary arteries and pulmonary release or inhibition of the uptake of vasoactive substances is likely a major factor in the constriction of pulmonary vessels associated with hypoxic ventilation, pulmonary edema, and pulmonary embolism (28). Under normal conditions, the pulmonary vascular bed is not exposed to excessive plasma serotonin because of the ability of platelets to store large quantities of serotonin and because plasma serotonin is rapidly metabolized by endothelial monoamine oxidase in the liver and lung (29). Increased plasma concentrations of serotonin may result from excessive production by enterochromaffin cells in the gastrointestinal tract, decreased lung uptake and metabolism, decreased uptake and storage of serotonin in platelets, or a combination of these conditions. One condition known to decrease the uptake and metabolism of serotonin in the lungs is exposure to halogenated inhalation anesthetics. Halogenated anesthetics have been shown to significantly inhibit serotonin removal from the pulmonary circulation in experimental models and halothane decreases the uptake and inhibits the metabolism of serotonin in the lung (30,31,32).

Taken together, a reasonable hypothesis is that exposure to fenfluramines may increase circulating levels of serotonin by affecting the platelet storage of serotonin. In most situations some of this excess serotonin is probably metabolized in the liver and lung. Exposure to halogenated anesthetics blocks the reuptake and metabolism of serotonin in the lung leading to a marked increase in the concentration of serotonin in the pulmonary circulation. Elevated serotonin concentrations may therefore reach a level high enough to cause pulmonary artery vasoconstriction leading to the development of acute pulmonary hypertension. Anesthesia and surgery in patients with pulmonary hypertension is associated with a high mortality especially if pulmonary artery pressure and pulmonary vascular resistance suddenly increase and right ventricular decompensation occurs (33,34). Although, pulmonary artery pressures were not measured and post mortem examination did not note morphological signs consistent with chronic pulmonary hypertension, the possibility that unrecognized pulmonary hypertension contributed to the fatal outcome in the patient described by Bennett and Eltringham cannot be excluded.

Although the aforementioned hypothesis seems plausible, it

must be emphasized that it is not yet clear if a drug interaction truly exists between anesthetics and fenfluramines. Adequately designed pharmacokinetic and pharmacodynamic studies are needed to definitively determine the effects of fenfluramines during the administration of inhaled anesthetics. However, until further information is available, prudence dictates that patients be free of these agents while undergoing anesthesia when possible. As recommended by Wyeth-Ayerst Laboratories (which markets both fenfluramine and dexfenfluramine) anesthesia should be administered with caution to patients taking fenfluramine and if general anesthesia cannot be avoided full cardiac monitoring and facilities for instant resuscitation should be provided (12).

In the meantime, clinicians should specifically inquire about the use of appetite suppressant drugs during the medication history and any suspected adverse drug events related to the use of anorexics alone or in combination with anesthesia should be reported to the manufacturer and the FDA.

Although the prescribing information for dexfenfluramine contains no warnings relating to general anesthesia, it might also be prudent to discontinue this compound prior to the administration of anesthesia until further information becomes available. Dexfenfluramine is hepatically metabolized to the active metabolite d-norfenfluramine. The elimination half-life of dexfenfluramine and d-norfenfluramine is 20 and 32 hours respectively. Therefore, dexfenfluramine should be discontinued at least 7 days prior to anesthesia. Since both fenfluramine and dexfenfluramine have been associated with a discontinuation phenomenon, it would be ideal to gradually taper the patient off these agents over several days such that the patient is free of drug at least a week prior to anesthesia (35,36,37,38,39).

Acknowledgments: The author is grateful for the assistance provided by Joseph Varon, M.D. and William Dana, Pharm.D.

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