Anesthetic Considerations for the New Anti-Obesity Medications

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Abstract

Combination drug therapy can effectively treat the problem of obesity. The most commonly used combination is a mix of fenfluramine and phentermine. Fenfluramine inhibits the reuptake of serotonin and acts on the hypothalmic appetite control center, while phentermine acts as an appetite suppressant. These drugs along with diet and exercise effectively help people to lose weight with few side effects. However, there are several anesthetic considerations when providing anesthesia services for patients on the fenfluramine and phentermine regime. Problems of hypotension on induction, hypoglycemia, hyperthermia and pulmonary hypertension have been reported in the literature.

Recently, dexfenfluramine (Redux) was approved by the U.S. Food and Drug Administration. It is the dextrostereoisomer of fenfluramine and is believed to produce the same weight loss with less side effects. Anesthesia providers must understand the potential risks involved when administering a general anesthetic to these patients.

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INTRODUCTION

Obesity has been called the number one public health problem in America. Several studies suggest that 25-34% of the adult population is obese.[1,2] Obesity is the second leading cause of preventable death in the United States, exceeded only by cigarette smoking.1 Approximately 30 to 40 billion dollars per year is spent by Americans on weight-loss treatments. Medical experts believe that they may have found a safe and effective weapon against the war on obesity.[3] The most commonly used combination of drugs directed at the problem of obesity is “fen-phen” a mix of fenfluramine (Pondimin) and phentermine (Ionamin). In addition, a dextrostereoisomer of fenfluramine (Redux) was recently released to replace the fen-phen mixture. All of these drugs in combination with diet and exercise facilitate weight loss with few side effects.3 However, caution must be exercised when providing a general anesthetic for this patient population.

OVERVIEW OF FENFLURAMINE AND PHENTERMINE

Fenfluramine is a sympathomimetic amine. It is unique in that it differs somewhat from the prototype drugs of this class used in the treatment of obesity.

The mechanism of action is unclear but may be related to inhibiting reuptake of serotonin or to increased glucose utilization. It appears to promote the rapid release of serotonin and may have serotonin receptor agonist activity. The drug may produce its main effect by acting on the hypothalmic appetite control center rather than changing glucose or lipid metabolism. Because it does enhance glucose uptake into skeletal muscle as well as suppress appetite, it has been of benefit to obese diabetic patients.[4] Fenfluramine is well-absorbed from the gastrointestinal tract

and the maximal anoretic effect is seen in 2-4 hours. The half-life is about 20 hours compared with 5 hours for amphetamines. Fenfluramine is excreted via the kidney and is pH-dependent. Fenfluramine appears to produce more central nervous system depression than stimulation.[5]

Contraindications to use include glaucoma, hypersensitivity to fenfluramine or other sympathomimetic amines, history of drug or alcohol abuse and psychotic illnesses. Fenfluramine should be used with caution in patients with hypertension or other types of cardiovascular disease including arrhythmias. Fenfluramine should not be administered during or within 14 days following the administration of monoamine oxidase inhibitors, since hypertensive crisis may result.5

Several cases of pulmonary hypertension have been reported in association with fenfluramine use. Recently primary pulmonary hypertension developed in a cluster of patients in France exposed to derivatives of fenfluramine in appetite suppressants.[6] In addition, fenfluramine may have catecholamine-depleting effects.5

Phentermine is an appetite suppressant structurally similar to amphetamines. It is also a sympathomimetic amine. However, it has significantly less sympathomimetic and stimulant activity than amphetamine. It is currently used as an anorexiant in conjunction with fenfluramine, exercise and diet for the short-term treatment of obesity in adults. Phentermine, like other anorexiants, stimulates the hypothalamus resulting in decreased appetite. Anorexiant effects are most likely mediated via norepinephrine and dopamine metabolism. When given as a single 3O mg sustained release dose, phentermine significantly reduced hunger and food intake in overweight individuals.[7] Phentermine is well absorbed and primarily excreted unchanged in the urine. A half-life of approximately 20 hours has been reported.5

Side effects include hypertension, tachycardia, psychological/physical dependence, psychosis and heat stroke. It is suspected that sympathomimetic amines can induce heat intolerance by increasing endogenous heat production.[8] The most common side effect is that of dry mouth. Central nervous system stimulation can occur manifesting as nervousness, increased tension, irritability, anxiety and insomnia. Tolerance can occur with anorexiants and usually occurs within 6-12 weeks. Increases in dose should not be undertaken in patients developing tolerance. When phentermine is prescribed alone, increasing the dose does not increase its effectiveness after tolerance has occurred. 5 8 [9]

Contraindications to use include arteriosclerosis, cardiovascular disease, hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, patients with a history of drug abuse, and during or within 14 days following monoamine oxidase inhibitors.9

Fenfluramine and phentermine are drugs that have been available since the 1970's. When prescribed alone, patients had difficulty tolerating the side effects of the drugs. Fenfluramine produced drowsiness and lethargy while phentermine produced stimulant properties of anxiety, nervousness and irritability. Subsequently, both drugs fell out of favor for the treatment of obesity. But when the non-stimulant anorectic fenfluramine was combined with the stimulant anorectic phentermine, a significant decrease in hunger was observed leading to weight loss among obese individuals without the side effects of lethargy or anxiety. 3 5 7 [10]

ANESTHETIC CONSIDERATIONS

There is an increasing number of articles in the literature related to the use of phentermine, fenfluramine and dexfenfluramine due to the popularity of the drugs. However, there is virtually no information available in the literature related to anesthetic considerations. Based on known pharmacology and preliminary observations there are several anesthetic considerations that would seem prudent involving patients using fenfluramine, phentermine, and dexfenfluramine.

Patients on these medications may frequently present for elective surgery including facelifts, abdominoplasties and breast procedures. Many patients on the fen-phen regime neglect to include the fenf luramine and phentermine in their list of prescribed medications during the pre-operative interview. Patients may not admit to taking these medications because of the stigma attached to obesity medications. Therefore, unsuspected problems such as persistent hypotension on induction, hypoglycemia and hyperthermia may result.

On induction, a persistent or prolonged hypotension, unresponsive to ephedrine, may occur. Fenfluramine has a catecholamine-depleting effect and first-line drugs such as ephedrine are ineffective because the patient lacks catecholamine stores.5 In these patients, the vasopressor of choice is a direct-acting vasopressor such as neosynephrine. With neosynephrine blood pressure may be restored to

acceptable levels.

In 1977, a single article appeared in the literature discussing a case report of a 23-year-old female admitted for elective dental surgery. She was known to have been taking her husband's fenfluramine up to the day prior to surgery. She was induced with thiopentone followed by suxamethonium and maintained on oxygen, nitrous oxide, and 2% halothane. Five minutes after induction, she became pulseless, cyanotic, and developed signs of acute pulmonary edema. She failed to respond to resuscitative measures including internal cardiac massage.

A study was then conducted using rabbits to demonstrate the response to inhalational agents and injected fenfluramine. Their results indicated that fenfluramine was a cardiac depressant rather than stimulant and patients concurrently receiving fenfluramine may be at risk when undergoing anesthesia with halothane. The study noted that significant amounts of fenfluramine and its active metabolites are found in the urine for six days after cessation of treatment. They recommend that the fenfluramine be stopped one week prior to general surgery.9

There does not appear in the literature any other guidelines regarding the discontinuation of the drugs prior to surgery. However, some consideration should be given to this concept and discontinuation of the drugs may be prudent.

The second anesthetic consideration is related to delayed gastric emptying. Horowitz found that a single dose of fenfluramine 40 mg significantly delayed gastric emptying of solid food in 8 obese patients (approximately a 15% reduction in the solid emptying rate) and may be partially responsible for the anorectic effect of the drug. However, fenfluramine has no significant effect on liquid emptying. Studies were conducted using only a single dose of fenfluramine, therefore, the effect of chronic administration and different doses of fenfluramine may further alter gastric emptying.[11] This study did not address the fact that delayed gastric emptying time is a recognized consideration in obese patients and did not state whether the 15% reduction time is in addition to their already altered gastric emptying time. Delayed gastric emptying time should be considered when planning an anesthetic for these patients especially if they have not discontinued the medication prior to surgery.

In diabetic patients, fenfluramine can potentiate the effects of insulin. Fenfluramine may increase the peripheral uptake of glucose or decrease the liver production of glucose.2 In noninsulin-dependent diabetes an oral hypoglycemic agent, fenfluramine produced a significant fall in fasting blood glucose levels and increased insulin sensitivity, without affecting insulin secretion.[12] In nondiabetic patients there is an increased risk of hypoglycemic reactions secondary to inadequate food intake related to the anoretic effects of the medication and increased glucose utilization.4 5 Therefore, monitoring for blood glucose during anesthesia for patients taking fenfluramine is advised.

Although rare, several cases of pulmonary hypertension have been reported following the use of fenfluramine. How fenfluramine may lead to pulmonary hypertension is unknown. Serotonin, a pulmonary vasoconstrictor has been implicated as it exerts a direct vasoconstrictor effect through potassium-channel blockade.[13] Elevated pulmonary arterial pressures may occur. Symptoms include progressive dyspnea, increasing restlessness, breathlessness, tiredness, chest pain, syncope, palpitations, edema and exercise intolerance. Dyspnea was the initial symptom reported in 91% of the cases frequently related to increasing exercise intolerance.

Upon discontinuation of fenfluramine and treatment with diuretics, in most cases symptoms resolved completely in 3-12 weeks.[14] However, there are reports of irreversible and fatal pulmonary hypertension in patients taking fenfluramine.13 The lack of research on this drug and its relationship to primary pulmonary hypertension is noteworthy. Therefore, patients should be advised to report immediately any deterioration in exercise tolerance.6 13 14 Pre-anesthetic interviews should include investigative questioning related to the presence of these symptoms pre-operatively.

Sympathomimetic amines, such as phentermine, can induce heat intolerance by increasing endogenous heat production as a result of CNS stimulation, and also as a result of impedance of dissipation of heat from the body by producing peripheral vasoconstriction.7 All patients should be properly monitored for hyperthermia.

DEXFENFLURAMINE

In April 1996, dexfenfluramine (Redux) was approved by the U.S. Food and Drug Administration for the long-term treatment of obesity. Dexfenfluramine is the dextrostereoisomer of fenfluramine and is believed to produce the same weight loss results with less side effects. In contrast to fenfluramine, dexfenfluramine is a relatively pure serotonin agonist, with minimal to no sympathomimetic

activity.5 Dexfenfluramine stimulates the release and inhibits reuptake of serotonin, leading to increased brain serotonin levels.5 Enhanced central serotoninergic activity selectively suppresses food intake. The potency of dexfenfluramine has been reported to be approximately twice that of fenfluramine in animal and human studies. Mechanisms other than central serotoninergic activity include dietary-induced thermogenesis, reduced gastric emptying time, decreased lipogenesis in adipose tissue, and lowering of the body weight "set-point". 5 [15] Dexfenfluramine has been shown to improve glycemic control in patients with noninsulin-dependent diabetes mellitus by improving fasting blood glucose and oral glucose tolerance by reducing hepatic glucose production.12 In addition to weight loss, dexfenfluramine has been shown to reduce blood pressure and serum cholesterol levels in obese patients.5 [16]

Side effects include tiredness, drowsiness, dizziness, mood disorders, sleep disturbances, dry mouth, nausea, diarrhea, constipation, and polyuria.15 It appears that dexfenfluramine is better tolerated than fenfluramine. Dexfenfluramine is prescribed alone thus avoiding phentermine 's side effects. However, the possibility of developing primary pulmonary hypertension remains a concern.5 6

Dexfenfluramine is new on the market and currently there is limited experience with patients taking the drug. It appears that the drug will be extensively prescribed. Special vigilance during pre-operative assessment to identify those patients on the medication is essential. In October 1996, anesthesia providers reported incidences of persistent and prolonged hypotension on induction of general anesthesia. In response to these reports, a news item appeared on CNN-TV in early November 1996 warning consumers and healthcare providers of the potential danger. The American Society of Anesthesiologists (ASA) issued a statement that they are aware and concerned about the reports of incidences of hypotension on induction of general anesthesia. The ASA stated that it is imperative that patients be forthcoming about any drug they have taken prior to surgery including all prescriptions and over-the-counter medications, such as diet pills, vitamins, and herbal preparations.[17]

Further experience with the new drugs and additional studies will be needed to fully appreciate the risks, side effects, and anesthetic considerations.

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