

Clinical Approaches to Male Infertility

With a Case Report of Possible Nifedipine-Induced Sperm Dysfunction

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Background: Male infertility has many causes, and recently it has been suggested that calcium channel blockers might contribute to male infertility.

Methods: A case consistent with nifedipine-induced male infertility is described. MEDLINE was searched for articles on the effect of calcium channel blockers and the general causes of infertility, with an emphasis on male infertility, using the key words "nifedipine," "male infertility," "sperm," and "calcium channel blockers."

Results and Conclusions: Male infertility induced by calcium channel blockers should be included in the differential diagnosis of infertile couples in appropriate cases. Whether a calcium channel blocker could be developed as a male contraceptive remains to be determined. Further studies are needed to determine the prevalence of infertility among men taking calcium channel blockers. (J Am Board Fam Pract 1997;10:131-6.)

Recent research indicates that calcium channel blockers can inhibit human sperm capacitation and prevent fertilization. Although known to those specializing in male infertility, this information is generally unknown to the general medical community.

Methods

A case consistent with nifedipine-induced male infertility is described. MEDLINE was searched for articles on the effect of calcium channel blockers on male fertility using the key words "nifedipine," "male infertility," "calcium channel blockers," and "sperm." MEDLINE was also searched for articles on male infertility in general with an emphasis on drug-induced male infertility. Specialty textbooks, along with the medical literature, were used to formulate a discussion of the infertility workup with an emphasis on male factors.

Effect of Calcium Channel Blockers on Male Fertility

Calcium channel blockers have been shown to have several detrimental effects on mammalian sperm. Verapamil caused decreased sperm density, lowered sperm motility, and decreased

adenosine triphosphate (ATP) concentration, as well as significantly lower egg penetration in guinea pigs.¹ Incubation of mouse sperm and eggs with diltiazem resulted in depressed fertilization without affecting sperm motility when compared with controls.²

Human sperm incubated in vitro with diltiazem (1 mmol) had decreased motility, but no effect on motility was found with lower concentrations of diltiazem (1 to 100 μ mol).³ Verapamil (5 to 50 μ mol) and nifedipine (1 to 100 μ mol) caused disruptive morphologic changes in head and tail regions of human spermatozoa, impaired motility, lower uptake of extracellular calcium, and decreased calcium-dependent adenosine triphosphatase (ATPase) activity.^{4,5}

When human sperm are ejaculated into the genital tract, they must undergo complex biochemical changes to prepare for attachment to the egg, a process known as capacitation. Evidence suggests that capacitation involves expression of a mannose lectin receptor on the sperm head that can attach to mannose on the egg's zona pellucida.⁶ Expression of this mannose lectin receptor is inhibited by calcium channel blockers.⁷ After attachment, the sperm head acrosome fuses with the sperm outer plasma membrane, and proteolytic enzymes are released. This acrosome reaction, which allows egg penetration, is mediated by long-acting calcium channels and inhibited by calcium channel blockers.^{7,8}

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In 1993 Benoff et al⁷ at North Shore University Hospital, Manhasset, NY, investigated a normospermic, infertile man whose motile sperm failed to fertilize human eggs in vitro. He was taking nifedipine for hypertension. His sperm became fertile after his medication was changed to an angiotensin converting enzyme (ACE) inhibitor. Subsequent in vitro investigation of sperm from 9 other infertile men taking calcium channel blockers for hypertension showed reduced capacitation and spontaneous acrosome reaction compared with fertile sperm. The sperm of 4 of these men recovered after the drug was stopped, and one couple achieved pregnancy. Benoff et al also showed that incubation of fertile sperm in vitro with either nifedipine or verapamil inhibited spontaneous acrosome reaction.

In 1995 the same group investigated and reported a case of another couple with male infertility secondary to nifedipine.⁹ The husband's sperm recovered after the drug was stopped, and the couple achieved pregnancy. While he was taking nifedipine, the husband's sperm had subnormal expression of mannose-specific lectin and did not exhibit spontaneous acrosome reaction in vitro. The sperm membranes from this man and other men on calcium channel blockers had higher baseline free cholesterol than did sperm membranes from fertile men.⁹⁻¹¹ In vitro experiments showed that capacitation involves reduction of the cholesterol content of the sperm plasma membrane. The investigators speculated that calcium channel blockers enter into the sperm plasma membrane, alter molecular packing, and reduce the rate at which cholesterol can leave the sperm plasma membrane under capacitating conditions. It is possible that other lipophilic drugs might affect sperm by a similar mechanism. Investigators from India reported evidence that human sperm incubated in vitro with nifedipine are more susceptible to lipid peroxidation and have dose-dependent reductions of membrane phospholipid and cholesterol content.⁵ This contrasts with the finding of Benoff et al of higher sperm membrane cholesterol in men on calcium channel blockers.

Case Report

Early in 1994 a 31-year-old woman, gravida 3, para 1, abortus 2, complained of inability to conceive despite 18 months of unprotected inter-

course. She was married to the same man who had fathered all earlier pregnancies. Thirty months before this visit, she gave birth to a full-term normal male infant by spontaneous vaginal delivery. Four years and 2 years earlier she had had spontaneous abortions, but she reported no history of pelvic infection, pelvic operations, or endometriosis. Although her menstrual cycles were slightly irregular, her basal body temperature calendar suggested ovulation and an adequate luteal phase. She was 5 feet 1 inch tall and weighed 130 pounds, had no evidence of systemic disease, and had normal breast development and normal hair distribution with no evidence of virilization. Findings on a pelvic examination were normal: she had no vaginitis, a parous cervix with no signs of infection, a normal-sized nontender uterus, no nodules of the uterine ligaments, and no adnexal masses.

Her 37-year-old husband had a 6-year history of hypertension. He had been prescribed Procardia (nifedipine) 90 mg/d 10 months prior to conception of their first child. He had no history of cryptorchidism, impotence, loss of libido, or difficulty with ejaculation. He did have mumps involving the parotid glands at the age of 16 years, but no history of orchitis. At his physical examination he weighed 190 pounds, was 6 feet 1 inch tall, had normal blood pressure, and had normal male hair pattern and secondary sex characteristics. Both testicles measured 5 cm in greatest dimension. No varicocele was observed with Valsalva maneuver. His phallus had a small benign-appearing nevus near the meatus, and there was no hypospadias. No abnormalities were palpated in the epididymis or vasa. He also had a history of mild intermittent transaminase elevations and an elevated serum ferritin. His liver was of normal size with no stigmata of cirrhosis. He reported no history of alcohol use, and serologic studies for hepatitis were negative. A liver biopsy showed no evidence of hemochromatosis, hepatitis, or cirrhosis. Semen analysis showed total volume 4.5 mL, complete liquifaction, sperm density 31,000,000/mL (normal > 20,000,000/mL, ideal > 40,000,000/mL), 72 percent motile (normal > 50 percent), and 87 percent normal morphology (normal > 50 percent).

The couple reported having intercourse on a regular basis during the fertile period of the cycle. Several cycles of clomiphene therapy were at-

tempted in the wife, but pregnancy was not achieved. Because of a newly reported (but generally known only to fertility specialists) association of nifedipine with male infertility, the husband's nifedipine was stopped, and his blood pressure was monitored. Six weeks later his wife became pregnant and subsequently gave birth to a normal male infant. The husband's hypertension recurred. Diuretic therapy was instituted, but it was ineffective and not well tolerated, so nifedipine was again prescribed.

Discussion

This and previous case reports suggest that nifedipine could interfere with male fertility, but there are few cases reported. Unfortunately, no in vitro studies were done to determine whether this man's sperm had reduced capacitation and spontaneous acrosome reaction, as was reported with other men on calcium channel blockers. The findings in this case suggest that nifedipine has only a partial contraceptive effect, as the patient initially was able to father a child while taking nifedipine, but later he was unable to father another child until nifedipine was stopped. His sperm count of 31,000,000/mL is on the low side of normal, which might be a separate cause of decreased fertility.

There are no large studies available to determine the prevalence of infertility among men taking nifedipine. The product information on Procardia was revised in September 1994 (and appeared first in the 1996 edition of the *Physicians' Desk Reference*)¹² to include the following statement of association with male infertility in humans:

Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum human dose. There is a literature report of reversible reduction in the ability of human sperm obtained from a limited number of infertile men taking recommended doses of nifedipine to bind to and fertilize an ovum in vitro. In vitro mutagenicity studies were negative.

Drugs and Male Infertility

Drugs can interfere with male fertility by affecting spermatogenesis (cytotoxic agents, nitrofurantoin, aminoglycosides, sulfasalazine, co-

trimoxazole), preventing erection (diuretics, β -blockers, etc), preventing ejaculation (ganglionic blockers), promoting retrograde ejaculation (α -adrenergic blockers) or by interfering with sperm capacitation or the acrosome reaction (calcium channel blockers).^{7,9-15} Libido can be diminished by dopamine blockers, such as thiorazine, or by drugs that interfere with testosterone. Anabolic steroid use causes suppression of the hypothalamic-pituitary axis with decreased follicle-stimulating hormones and leutinizing hormones, resulting in lowered sperm counts. Spironolactone, colchicine, allopurinol, cimetidine, and cyclosporine have been associated with male infertility. Alcohol, drug abuse, and central nervous system depressants can decrease male sexual desire and performance.

The workplace environment is a potential source of male infertility. The nematode pesticide dibromochloropropane has been associated with lowered sperm count in California pesticide manufacturing workers and banana workers.^{16,17} Ethylene glycol (antifreeze) metabolites are toxic to sperm.¹⁸ In smelter and battery factory workers, increases in serum lead correlate with decreased sperm count, lowered motility, and abnormal morphology.¹⁹

Infertility Workup With Emphasis on Male Factors

Physicians need to take a complete history of both partners when evaluating infertility (Table 1).²⁰ Physical examination in the male patient should focus on hair pattern, penile meatus size and location, prostate, seminal vesicles, testicular size (normal long axis > 4 cm), any epididymal induration suggesting obstruction, presence or absence of the vasa, presence of varicocele when standing with Valsalva maneuver, anosmia, and visual fields. Routine laboratory testing in the man includes complete blood count, semen analysis, urinalysis, and VDRL. Testosterone, follicle-stimulating hormone (FSH), and prolactin levels, chromosome analysis, vasogram, and testicular biopsy can be indicated as secondary tests.

The routine workup for the woman includes an examination focusing on secondary sex characteristics, presence of galactorrhea, evidence of virilization (hair pattern), complete and thorough pelvic examination, complete blood count, Papanicolaou smear, urinalysis, VDRL, and basal body

Table 1. Infertility History.**Relationship**

Duration of infertility
 Fertility in previous relationships
 Frequency of intercourse
 Coital techniques
 Use of lubricants
 Impotence

Adult illnesses

Acute viral or febrile illness in past 3 months
 Mumps orchitis
 Renal disease
 Radiation therapy
 Sexually transmitted disease
 Stress and fatigue
 Tuberculosis
 Other chronic disease

Occupation and habits

Exposure to radiation, chemicals (lead, ethylene glycol, dibromochloropropane, etc), or excessive heat (saunas, hot tubs, etc)

Childhood illnesses

Cryptorchidism
 Timing of puberty

Surgery

Herniorrhaphy
 Retroperitoneal surgery
 Tubal ligation
 Vasectomy

Drug use

Drugs affecting spermatogenesis: alkylating agents, nitrofurantoin, sulfasalazine, co-trimoxazole
 Drugs affecting erection: diuretics, β -blockers, others
 Drugs causing retrograde ejaculation: α -adrenergic blockers
 Drugs inhibiting capacitation: calcium channel blockers
 Drugs suppressing hypothalamic pituitary axis: anabolic steroids
 Drugs decreasing libido: dopamine blockers, drugs that interfere with testosterone, alcohol, drug abuse, central nervous system depressants
 Miscellaneous drugs: spironolactone, colchicine, allopurinol, cimetidine, cyclosporine

Review of systems

Focus on endocrine systems (diabetes, thyroid disorders)

Gynecology

Contraceptive use
 Diethylstilbestrol use by mother
 Douches
 Menstrual history
 Pelvic inflammatory disease (history, recent, or past symptoms, might be asymptomatic)
 Previous pregnancies

Modified from Frey²⁰

temperature recording. Specialized tests might include the postcoital test, hysterosalpingogram, laparoscopy, endometrial biopsy, and serum progesterone measurements. Detailed explanations of specialized workup and treatment of female infertility is beyond the scope of this article.

There are multiple causes of infertility, and 10

to 30 percent of couples have more than one.²⁰ Frequent causes include male factors (in 18 to 31 percent of infertile couples), ovulatory dysfunction (16 to 30 percent), tubal damage (12 to 16 percent), endometriosis (5 to 25 percent), cervical mucus abnormalities (3 to 5 percent), and unexplained factors (13 to 28 percent). Twenty percent of couples will have both a male and female factor contributing to infertility.

Male factors include varicocele, oligospermia or azospermia, obstruction of sperm flow, erection or ejaculation problems, improper coital techniques, semen antisperm antibodies, disorders of sperm function or motility (asthenospermia), and disorders of sperm morphology (teratospermia).

Varicocele is a dilatation of the venous plexus of the scrotum and spermatic cord. Varicocele is very common, occurring in 15 to 20 percent of the male population. Most varicoceles are left-sided resulting from incompetent venous valves of the left internal spermatic vein, which allows gravity-dependent retrograde blood flow from the left renal vein into the scrotal venous plexus. Most men with varicoceles have normal fertility. Varicoceles are found in about 35 percent of men with primary infertility and 81 percent of men with secondary infertility.²¹ Varicoceles, particularly large varicoceles, can cause a progressive injury to the seminiferous epithelium. Correction of varicocele is associated with improved sperm count in 60 to 80 percent of cases.²² Reported pregnancy rates after varicocelectomy vary from 20 to 60 percent.²¹

Congenital obstruction of sperm flow is suggested by azospermia, normal FSH and testosterone levels, and a testicular biopsy showing normal spermatogenesis. Sometimes pregnancy can be achieved with microsurgical techniques.

Vasectomy reversal, or microsurgical vasovasotomy, results in sperm in the ejaculate in about 85 percent of cases, and a pregnancy rate of 50 to 55 percent according to the results of the Vasovasotomy Study Group.²³ The procedure can be done under local anesthesia with conscious sedation. In certain cases the distal vas will need to be anastomosed to the epididymis because of epididymal obstruction. Vasoepididymostomy is a technically demanding procedure and usually requires general or spinal anesthesia.²¹ Causes of epididymal obstruction include infection, long-standing previous vasectomy, trauma, congenital anom-

aly, and perhaps a mild variant of cystic fibrosis.

Sperm flow can be obstructed at the level of the ejaculatory ducts, which can be visualized with transrectal sonography. The obstruction can be anatomic and amenable to transurethral resection.²⁴ Functional obstruction might result from various neurologic disorders discussed later in this article.

Disruption of the hypothalamic-pituitary-gonadal axis leads to understimulation of the testis, impotence, and infertility. One third of chromophobe pituitary tumors make prolactin, suppressing the hypothalamic gonadotropin pulse generator.²² Abuse of anabolic steroids will suppress FSH, and spermatogenesis will not be stimulated.

Klinefelter syndrome results from two X and one Y chromosomes. These men have small testes, sometimes gynecomastia, and variable testosterone levels. The patients vary in appearance from severely eunuchoid to fully masculinized with small testes. Buccal smear is positive for sex chromatin, chromosomal analysis reveals the extra X chromosome, testosterone is usually low, and FSH is high.

The Sertoli-cell-only syndrome results from the absence of germ cells in the testis, which can be found by testicular biopsy. The testis might be smaller, and there might be a defect on the long arm of the Y chromosome. In the germ-cell-arrest syndrome, testicular biopsy shows that spermatogenesis is arrested at a given stage. Kartagener syndrome (immotile cilia syndrome) is the triad of infertility, bronchiectasis, and situs inversus. The sperm tail is immotile, as are the respiratory cilia, secondary to a defect in the protein dynein. This protein is part of the microtubular assembly that gives the sperm tail and respiratory cilia mobility.

Various neurologic disorders can affect erectile function and ejaculation. Antegrade ejaculation requires coordination of emission of semen, contraction of the bladder neck, and contraction of the bulbocavernosus, ischiocavernosus, and pelvic floor muscles. Emission and bladder neck contraction are controlled by the sympathetic ganglia from T-10 to L-2. Subsequent contraction of the other muscles of ejaculation is mediated by the parasympathetic nervous system. Retrograde ejaculation and anejaculation can result from diabetic autonomic neuropathy, multiple sclerosis, or surgical interruption of sympathetic nerves (eg,

retroperitoneal lymph node dissection). Retrograde ejaculation is diagnosed by examination of postorgasmic urine for sperm. Retrograde ejaculation can be treated medically with a 2-week trial of sympathomimetic agents, such as pseudoephedrine 60 mg four times a day, or by collection of postejaculation urine with sperm concentration and intrauterine insemination.

Spinal cord injury patients usually are unable to ejaculate, and some may be treated with artificial electrical stimulation of ejaculation. Some spinal cord injury patients are able to lead productive lives; they marry and some desire children. Although sperm obtained from electrical stimulation of ejaculation from spinal cord injury patients is generally of poor quality, an overall pregnancy rate of 37 percent has been reported with an average of 3.5 electrical stimulations of ejaculation per patient.²⁵ A special probe is inserted into the rectum of the patient with spinal cord injury, and a rhythmic current is applied to cause erection and ejaculation. Often retrograde ejaculation occurs, and this sperm is collected with urethral catheterization. Complications include rectal burns (rare), muscular contractions, and autonomic dysreflexia.

The most common cause of male infertility is idiopathic oligospermia (< 50,000,000 sperm per ejaculate) and asthenospermia (< 50 percent motile sperm). Various treatments have been reviewed by Howards.²⁶ Unproved but possibly helpful medical treatments include pulsatile gonadotropin-releasing hormone, human chorionic gonadotropin, clomiphene citrate, tamoxifen, testolactone, and mesterolone.

Another approach to male infertility is sperm processing and intrauterine insemination. These procedures can be used when antisperm antibodies are present or when there are abnormalities of semen volume, liquifaction, or viscosity.

Assisted reproduction techniques include in vitro fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, and intracytoplasmic sperm injection (ICSI). ICSI involves injecting a single selected sperm through the oocyte zona pellucida and cytoplasmic membrane with a micropipette under microscopic visualization. A preliminary pregnancy rate of 46 percent was reported by Palermo et al.²⁷ It is possible that ICSI will become the most effective treatment for idiopathic oligospermia and asthenospermia.

Conclusion

There are many causes of infertility, and there can be multiple causes in one or both partners. This case study suggests but does not prove that nifedipine might contribute to male factor infertility. If the male partner of an infertile couple is taking nifedipine, verapamil, or diltiazem, another drug should be substituted that would not interfere with fertility. ACE inhibitors are an appropriate alternative for hypertension.

Perhaps in the future a calcium channel blocker or other drug will be developed that reversibly and reliably inhibits sperm function with acceptable side effects. Further studies are needed to know the prevalence of infertility among men taking calcium channel blockers.

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