OCULAR SAFETY OF VIAGRA, (SILDENAFIL CITRATE)*

BY Alan M. Laties, MD AND Frederick T. Fraunfelder, MD

ABSTRACT

To date, sildenafil citrate (Viagra) gives every evidence of being a safe drug for the eye despite a series of expressed concerns. A review of how its ocular safety profile has been identified offers insights into the strengths and weaknesses of present systems and resources for judging the ocular safety of Viagra or, for that matter, of any new drug. Such insights include:

- The great value of careful, informed assessment of preclinical information gleaned from laboratory experiments. By and large, such assessments point the way toward appropriate clinical evaluation. For Viagra, early in its development it was noted that besides exerting a major inhibitory effect on the intended target, the vascular-associated enzyme phosphodiesterase 5 (PDE5), the drug also exerts a lesser but definite inhibitory effect on the closely related PDE6, located in the retina. For this reason, preclinical evaluation of the drug included electroretinography plus postmortem histology. In addition, an extended eye examination was incorporated into clinical protocols.
- The often chaotic but invaluable information stream that becomes available once marketing approval has been gained and large populations begin to use a drug. False alarms, misattribution, and erroneous information are the order of the day. Nevertheless, as information accumulates, patterns of response clarify and the true nature of special susceptibility for subpopulations, if any, becomes apparent.
- A role for the astute clinician remains: Subtle changes or unusual risks for subpopulations can be missed entirely for long periods of time.
- A manifest need for improvement in evaluation of postmarketing side-effects. This need has led to the establishment of a new discipline: pharmacoepidemiology. In ophthalmology, the National Registry of Drug Induced Ocular Side-Effects maintains a constant and invaluable surveillance.

* From the Scheie Eye institute, Philadelphia (Dr Laties) and Casey Eye Institute, Department of Ophthalmology, Oregon Health Sciences University, Portland.

Examples are supplied to illustrate each of these major points: Our presentation will include data gleaned from clinical trials plus postmarketing information on the incidence, duration, and type of color vision defects observed at different doses of Viagra.

INTRODUCTION

Viagra (sildenafil citrate) is the first of a new class of orally effective treatments for erectile dysfunction.[1] It potently inhibits cGMP-specific phosphodiesterase type 5 (PDE5) (Fig 1), found in high concentrations in the

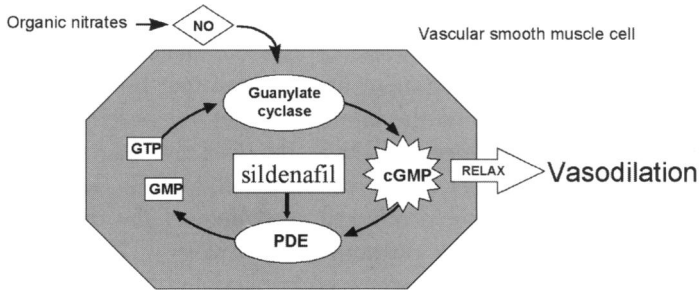

FIGURE 1

Actions of sildenafil citrate. Mechanism of endothelium-dependent vasodilatation and effect of organic nitrates and nitric oxide (NO) donors. cGMP, cyclic guanosine monophosphate; PDE, phosphodiesterase.

smooth-muscle cells of corpus cavernosum and in lesser concentrations in blood vessels of the systemic circulation.[2,3] Because of its ability to act as a mild vasodilator, sildenafil was originally investigated as an antianginal agent, but that course of investigation was abandoned. Sildenafil also weakly inhibits PDE6 (Table I).[4] PDE6 is present in high concentrations in cone and rod cells .[3] Sildenafil has a plasma half-life of about 4 hours and a time to peak plasma concentration of 1 hour.[5] Abnormal vision,

TABLE I. SELECTIVITY OF SILDENAFIL FOR HUMAN PDES

ENZYME	AFFINITY	SUBSTRATE	
PDE1	290 nM	CAMP	cGMP
PDE2	68,000 nM	CAMP	(cGMP)
PDE3	17,000 nM	CAMP	
PDE4	7,300 nM	CAMP	
PDE5	3.9 nM		cGMP
PDE6	38 nM		cGMP

described as a blue tinge to vision or an increased brightness of lights, has been reported by 3% of patients treated with sildenafil in flexible-dose studies.[6] In trials where subjects received fixed doses of sildenafil (5 to 200 mg) from the beginning of the study, the reports of abnormal vision were

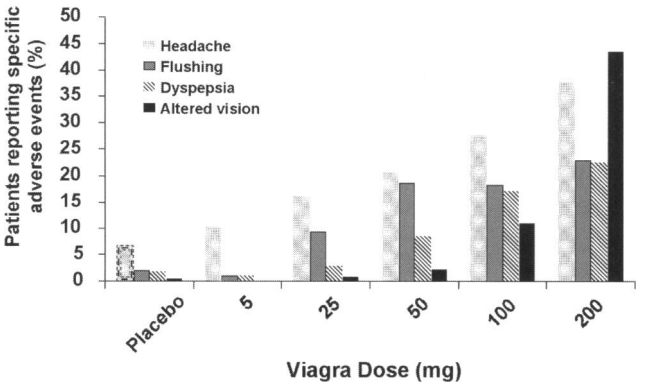

FIGURE 2

Percentage of patients reporting specific adverse events (all causes) enrolled in placebo-controlled, fixed-dose studies during clinical development program of sildenafil citrate. Incidence of abnormal vision increases with increasing dose (n = 1,741).

found to be dose-dependent (Fig 2). The effects of sildenafil on vision are likely due to inhibition of the retinal PDE6 isozyme.[7]

BACKGROUND: THE DEVELOPMENT OF VIAGRA

Early in preclinical development, it was found that sildenafil inhibits retinal PDE6 enzymes with an IC50 of 27-58 nM.[4] Although this was substantially less than its effect on the intended target, PDE5 (IC50 3.9 nM), it led to the evaluation of safety of high doses of sildenafil on retinal histopathology in rats and dogs and on electroretinograms (ERGs) in the dog.[8] To assess toxicologic effects, oral sildenafil (60 mg/kg, or approximately 50 times the maximum human recommended dose) was administered to rats daily for 6 months. No histopathologic evidence of toxicity was observed to the eye or visual pathways after long-term exposure to high doses of sildenafil. Likewise, when oral sildenafil was administered daily to dogs for 12 months (80 mg/kg, or approximately 65 times the maximum human recommended dose), there was no histopathological evidence of toxicity to visual pathways. Thus, in long-term testing in the rat and dog, there was no evidence of any toxicologic effect on the retina .[8]

In the dog, the concentrations required for a threshold ERG effect

were equivalent to a 400 mg dose in man or four times the highest recommended therapeutic dose. Free plasma sildenafil levels of 51 to 540 ng/mL induced dose-related increases in the implicit time of the a- and b-wave and reduced the amplitude of the a-wave of ERGs (Fig 3). All

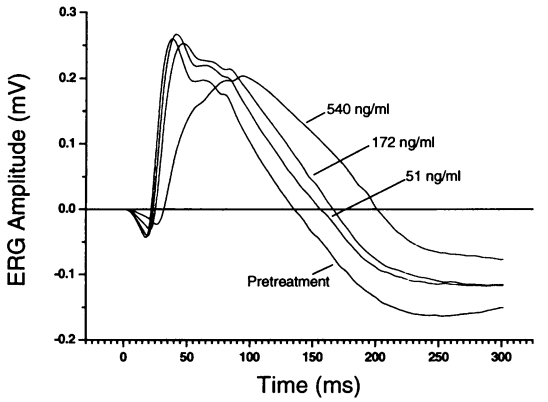

FIGURE 3
Effects of intravenously administered sildenafil citrate on electroretinogram (ERG) evoked by a flash (50 μsec) of blue light on the dark-adapted anesthetized dog. Each curve represents average response to five consecutive light challenges.

effects on ERGs were transient and reversible. They declined in a manner consistent with the plasma half-life of sildenafil.[8]

CLINICAL STUDIES

Cognizant of the preclinical data, substantial efforts were made to investigate the visual effects of sildenafil during clinical development. A number of Phase II and III studies were carried out to determine the safety of sildenafil in relation to the retina and visual function. Much of the data, with complete study descriptions, will appear in print shortly. Initially, short-term studies were performed to investigate the acute effects of sildenafil on the eye. These were followed by much longer studies to determine the consequences of chronic exposure of sildenafil on retinal function.

ACUTE STUDIES

The first study examined the effects of increasing doses of sildenafil on the results of several visual function tests.[9] A double-blind, placebo-controlled, crossover, Phase II study assessed the acute effects (1 to 24 hours)

of sildenafil (50 to 200 mg) in 16 healthy male volunteers. Sildenafil did not produce clinically significant changes in visual acuity, electroretinograms, intraocular pressure (IOP), contrast sensitivity, or pupillometry measurements compared with placebo. However, at single oral doses of 100 and 200 mg, transient impairment of color discrimination in the blue/green color range was detected using the Farnsworth-Munsell (FM) 100 hue test. These effects were fully reversible, and dose-related and occurred near the time of peak plasma concentration (1 to 2 hours after dosing).

A second study using only a single supratherapeutic dose (200 mg) of sildenafil in 8 healthy volunteers produced no clinically significant effects on visual field, visual acuity, photostress test, IOP, and ERGs. However, a modest increase in error score on the FM-100 hue test (blue-green) was again evident 1 to 2 hours postdose, resolving within 5 hours of dosing.[10]

In a third study, 8 patients with early age-related macular degeneration were tested for the acute effects of 100 mg of sildenafil. The study was placebo-controlled, randomized and double-blind with cross-over design. The patients underwent a battery of tests that included visual acuity, Humphrey perimetry, color discrimination D15 test, photostress, and Amsler grid. A detailed description of study results is just now in preparation (Data on file, Pfizer Central Research). However, in brief summary, they disclosed no special susceptibility as the study medication had little to no effect on visual performance in any of the subjects.

LONG-TERM STUDIES

Patients with erectile dysfunction and no history of eye disorder are described in detail elsewhere. Morales and associates[6] have summarized the clinical safety of sildenafil in phase II/II clinical trials. In 6 flexible-dose studies comparing the efficacy of sildenafil (734 patients) with placebo (725 patients), abnormal vision was reported by 3% of those treated with study drug and 0% of those given placebo. The visual disturbances were most often described as a bluish tinge to vision or an increased brightness and sensitivity to lights. In 10 long-term, open-label extension studies involving 2,199 patients, the reported incidence of abnormal vision was somewhat lower (2%). A 52-week clinical trial conducted in 47 patients with erectile dysfunction was designed to monitor the long-term effects of sildenafil on visual function.[9,10] Patients initially received sildenafil on a fixed-dose schedule (50 to 200 mg as needed) for 12-weeks, followed by a 40-week open-label flexible-dose period (25 to 100 mg as needed). Visual function was tested at baseline, 12 weeks, and 52 weeks.

Patients were not required to take a dose of sildenafil on the morning of their clinic visit; consequently, any changes to the visual function test results represented long-term rather than acute effects of sildenafil. No clinically significant changes were seen in visual acuity, contrast sensitivity, FM-100 hue test, photostress test, and slit-lamp examination. No serious visual adverse events or discontinuations occurred because of visual adverse events.

Concerning IOP, a strange focal cluster of 6 reports of "glaucoma" were issued from a single town in Germany prior to approval of the drug within that country (World Wide Safety, INTELRSG, 1998). Despite wide use of the drug within the United States and abroad, only occasional reports of glaucoma have been received. With respect to glaucoma, careful attention was paid to both the pupil and IOP during clinical development. For example, in 8 healthy male subjects receiving supratherapeutic doses of sildenafil, there was no significant change in IOP 0.75 hours postdose.[10] Monitoring of both pupil diameters and IOP during several clinical trials in the United States and abroad failed to demonstrate any effect whatsoever of sildenafil on either. In fact, as a demonstration of both the nature of single-event reporting and the inherent difficulty of attributing an event to the intake of a drug, a single report of an apparent cure of a 70-year-old patient with glaucoma of 9 years duration after sildenafil represents the most thoroughly documented case of an effect of sildenafil on IOP. Because medical therapy was insufficient to bring his pressure into the normal range, he required laser surgery, after which his pressures were serially recorded as 18 OD 19 OS applanation. Some time later, having taken a total of only three 100-mg doses of sildenafil, the patient returned to his ophthalmic consultant to find that his pressures now were 14 OD 13 OS applanation (personal communication, Dr Murray Maytom, Pfizer Inc) In the words of his ophthalmologist, "Based on the evidence at hand, one would be reluctant to give the credit to sildenafil, but as far as I can understand from the patient it has been the only factor that had changed or could have had an influence on what previously had always been a fairly stable problem."

LONG-TERM STUDIES: SUBPOPULATIONS

A retrospective analysis of combined data from 18 phase II/III studies (fixed- or flexible-dose, 4 to 26 weeks) evaluated visual adverse events in patients receiving sildenafil (5 to 200 mg) for the treatment of erectile dysfunction.[11] Of the 2,722 patients who received sildenafil and the 1,552 patients who received placebo, 66 patients also had a history of eye

disorders, which were described as diabetic retinopathy, glaucoma, and macular degeneration. A total of 9 visual adverse events were reported for these 66 patients, 7 from the 39 patients treated with sildenafil and 2 from the 27 patients treated with placebo. Of the 39 patients who received sildenafil, only 1 patient discontinued treatment because of a visual adverse event. This patient experienced moderate blurred vision and discontinued treatment with 10 mg of sildenafil on day 8 of treatment. Overall, sildenafil was generally well tolerated in this limited sample of patients with a history of eye disorders.

POSTMARKETING INFORMATION

Sildenafil has been approved in over 50 countries. As of November 1998, 6.4 million prescriptions had been filled within the United States, representing over 50 million tablets dispensed. This equates to over 3.5 million men and corresponds to a cumulative exposure of 25 million man-weeks since the drug was launched in April 1998. To help track potentially important adverse events following the release of new drugs, the Spontaneous Reporting System has been developed.[12] Spontaneous reports are based on a worldwide reporting system. Initially, reports are made to a manufacturer, a regulatory body, or both. They are received from multiple sources, including healthcare providers, consumers, media registries, the literature, and lawyers. Reports are received that may be duplicates, may be poorly detailed, or may even be spurious. Despite these limitations, the system is important to both manufacturers and regulators worldwide and is a necessary part of monitoring drug safety. Spontaneous reporting is the primary method of signal detection for events that occur at a very low incidence rate.[13,14]

A scattering of visual reports related to sildenafil have been received by the Food and Drug Administration; these include diplopia, temporary vision loss or decreased vision, ocular redness or bloodshot appearance, ocular burning or pain, eyelid swelling, increased IOP, retinal vascular occlusion or bleeding, vitreous detachment or traction, and paramacular edema.[15] Overall, the lack of either pattern or concentration of finding is reassuring.

Once received, reports are recorded on standard MEDWATCH forms. Both the FDA and the manufacturer retain copies. Under the Freedom of Information Act, the FDA office of Postmarketing Drug Risk Assessment in the Center for Drug Evaluation Research will supply a summary of all adverse events recorded for an individual agent upon appropriate request. Moreover, by specific request, copies of individual case

safety reports can also be obtained. The FDA prefaces its summary of adverse events with a thoughtful guide to interpretation. This guide emphasizes, among other factors, inadequacies of the system as regards underreporting and misassignment of cause and lack of complete information about the actual number of drugs taken and their dosage and about the severity and nature of underlying disease. For ophthalmology, a special resource is available. The National Registry of Drug Induced Ocular Side-Effects not only receives individual reports from ophthalmologists and other health professionals concerning ocular adverse events but also maintains a continuous international surveillance. This surveillance includes reports from the world's literature, from the Spontaneous Reporting System of the World Health Organization, and from the FDA. The results are disseminated by publication in *Drug Induced Ocular Side-Effects*.

As mentioned previously, reported ophthalmic adverse events following sildenafil are relatively few and broadly distributed. In confirmation of observations made during clinical development, external signs and symptoms characteristic of conjunctival vasodilatation are reported. These present variously as conjunctival injection, ocular redness, bloodshot appearance, and ocular burning. Two instances of extraocular muscle paresis have also been documented. One case was reported recently in the *American Journal of Ophthalmology*.[16] In this instance, a pupil-sparing third nerve paresis occurred 36 hours after a 56-year-old man with preexisting microvascular disease took a 50 mg dose of sildenafil. The second case, available through MEDWATCH, involved a sixth nerve palsy in a 76-year-old man with diabetes.

Within the eye, posterior vitreous detachment, retinal hemorrhage, and vascular occlusion have all been reported, most commonly in individuals with preexisting diabetes mellitus. These reports are infrequent. As is common in such instances, reasonable attribution of cause requires the emergence of a clear pattern of clinical event related to drug ingestion. In effect, for a clear "signal" to emerge, it must overcome the "noise" of expected incidence in the absence of drug ingestion. At present no such clear signal of serious pathology from sildenafil has emerged. For attribution of vascular events to sildenafil, the need to distinguish true drug effect from unaccustomed exertion during sexual arousal adds a level of complexity.

Adverse events related to PDE6 inhibition are most often recorded as "abnormal vision," recovered without specification as to whether the visual disturbance related to a color deficit, enhanced brightness, or altered visual acuity. Since the events are transient, fully reversible, and not

unexpected, underreporting is manifest. As a caution, out of concern that a selective susceptibility may be present, those with hereditary retinal degenerations are warned of special risk in the drug label.[15,17]

Also consistent with data obtained during clinical development are 2 recent studies. In one, Vobig and associates[18] found that a 100 mg oral dose of sildenafil in 5 healthy men did not affect visual acuity, color vision, IOP, visual field, or visual evoked potential. The a- and b-wave amplitudes of the ERG were moderately reduced 1 hour after drug administration, returning to normal within 6 hours. Scotopic and photopic implicit times were not significantly altered. Zrenner[19] has estimated that the recorded diminution in b-wave amplitude corresponds to a loss in light sensitivity of 0.2 log units, or approximately equivalent to the light-absorbing effect of a car windshield. A second report, available only in abstract form at present, also documents the acute effects of sildenafil.[20] Six patients with erectile dysfunction were tested before and then 1 to 3 hours after taking a 100 mg oral dose of sildenafil. In this series, the implicit time of the scotopic ERG was selectively lengthened while the scotopic wave amplitudes and the entire photopic ERG were spared. P 100 implicit times for the visual evoked potential did not show any significant change. Of great interest, 3 patients describing color vision disturbances were found not only to have intact visual acuity and visual field but also to have only slightly increased errors in Farnsworth panel tests. The investigators suggest that therapeutic doses of sildenafil have minor acute effects on visual function, with the rod photoreceptors preferentially affected.

Despite the best intentions of both the FDA and pharmaceutical companies, flaws are evident in the evaluation of drug side effects. Some, such as underreporting, are unavoidable.[13] One deserves special mention: inadequate follow-up to individual MEDWATCH reports. The information on the MEDWATCH form frequently is insufficient to permit a considered judgment; often it just is not possible to arrive at valid conclusions in the absence of a detailed case description. And unfortunately, despite best efforts by either the FDA or a pharmaceutical company, full details are often unobtainable.

For ophthalmology, the situation is partially alleviated both by the existence of the National Registry for Ocular Side Effects and also by a long-standing tradition of informative case reporting in ophthalmic journals. Thus, the discovery that the beta-blocking agent practolol could cause an oculomucocutaneous syndrome serves as a clear illustration of a serious adverse event brought to clinical attention by this means.[21] Similarly, the report of mental aberrations, temporary in nature, following local instillation

of cyclopentolate eye drops, illustrates clinical discovery of a less serious adverse event.[22] In both instances, astute clinical observation led to a case report that enhanced clinical awareness.

CONCLUSIONS

Overall, current clinical data suggest that treatment with sildenafil can cause short-term, transient, reversible effects on color discrimination in the blue-green range with few if any clinically significant effects on other acute visual function tests. No clinically significant pattern of effects following long-term administration is presently recognized.

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DISCUSSION

DR ALLAN J. FLACH. I want to thank the authors and the American Ophthalmological Society for inviting me to discuss this excellent paper. In my opinion, Dr Laties and Dr Fraunfelder have done a fine job reviewing the background and development of sildenafil citrate (Viagra, Pfizer). They have provided us with a nice summary and discussion of the clinical developments reflected in short- and long-term studies concerning both healthy volunteers and patients with adult-related macular degeneration. These clinical investigations appear to be well designed in that they include prospective studies that are randomized and placebo controlled. Furthermore, the authors have reminded us of the importance of postmarketing surveillance. They have provided us with a good discussion of the strengths and weaknesses of our present system. We are indeed fortunate to have not only the Spontaneous Reporting System (SRS) but also the National Registry of Drug-Induced Ocular Side Effects, which is unique to our profession.

It is clear to me from the studies that are discussed by the authors that sildenafil can cause transient, subtle changes in vision often described as blue/green color deficits and enhanced brightness in 2% to 3% of the treatment population. Therefore, although the drug should be used with caution in patients with retinal degenerations and certain rather rare enzyme deficiencies as outlined by the authors, the drug appears to be relatively safe for the vast majority of our population.

As the authors suggest, the postmarketing surveillance efforts have reported ocular events that may or may not be related to the use of sildenafil. These events include diplopia, extraocular paresis, decreased vision,

conjunctival vasodilation, ocular burning, ocular swelling, retinal hemorrhages, posterior vitreous detachment and macular edema. However, the association of these findings to the use of sildenafil remains to be established. For example, 15 years ago, I examined a patient who complained of the acute onset of a subtle change in the central vision of one eye, which was associated on examination with an isolated macular hemorrhage in this eye. This case taught one of our residents two important things. First, physical exertion can cause a retinal hemorrhage. Second, it is important to close the examination room door while taking social histories. In this case, after a long discussion with the patient in an attempt to identify the origin of the hemorrhage, the patient commented that the change in his vision was noted soon after he had experienced the "best sex of his life." His wife immediately walked into the room through the open door exclaiming, "and who was that with dear?" Two months after the divorce, we completed our workup of the patient and ruled out all other potential etiologies for the macular hemorrhage other than unaccustomed exertion during sexual arousal. Therefore, I think it is very wise for Dr Laties and Dr Fraunfelder to caution us within their manuscript, "For attribution of vascular events to sildenafil, the need to distinguish true drug effect from unaccustomed exertion during sexual arousal adds a level of complexity."

Myocardial infarctions have been reported in patients using sildenafil.[1] If patients suddenly begin to dramatically increase their physical activity, it is not surprising that those unaccustomed to this exertion and in borderline physical condition may have cardiovascular accidents. The recognition of this clinical experience suggests that it is prudent that we attempt to anticipate potential ocular toxicities that might be encountered with the widespread use of sildenafil. This brings to mind a seldom-read and rarely quoted article entitled, "Ophthalmodynia Hypertonica Copulationis: A New Syndrome?"[2] This report describes a man who experienced the symptoms of an attack of angle-closure glaucoma each time he had intercourse in a darkened room while he was in a prone position. The publication was clearly viewed as a seminal article by one of our most prominent Society members who complimented the author on his new finding with the note, "Congratulations on your new SINdrome!" signed R.S. (personal communications, Andrew Markovits, MD). This note was sent to the author exactly 10 years prior to this member's election as president of this Society and 11 years prior to his receiving the Howe Medal. I have always thought of this as the darkroom prone provocative test PLUS. It may be important for us to remember that as we age, our lenses increase in their volume by as much as 30%, often with an associated narrowing of the angle.[3] These

anatomic changes may be accompanied by a further narrowing of the angle induced by the acute changes in the iris and ciliary body related to the increased ocular autonomic nervous system activity that accompanies sexual activity. Therefore, I think it is important for us to be aware of the existence of this darkroom prone provocative test PLUS and its potential relationship to sildenafil use in an effort to avoid an epidemic of unplanned and possibly unrecognized positive tests.

There is a great potential for overuse and abuse of sildenafil. By carefully taking past medical histories we can help rule out the existence of many diseases and conditions that are accompanied by impotence and that have more specific treatments, such as diabetes mellitus with a hormonal etiology; neurologic diseases; chronic renal, hepatic, and thyroid disorders; alcohol abuse; and psychiatric diseases. It is particularly important for us to remind our internal medicine colleagues that topical beta blocker and oral carbonic anhydrase treatments can cause impotence.[4]

Finally, we should be alert to potentially harmful drug interactions. The potential synergism between vasodilators such as the organic nitrates (amyl nitrite, nitroglycerin, isosorbide dinitrate, erythrityl tetranitrate, pentaerythritol tetranitrate) and possibly calcium channel blockers (diltiazem, nicardipine, nifedipine, nimodipine, verapamil) with sildenafil can result in changes in blood flow that can be life-threatening.[5] It would seem to be important for us to attempt to anticipate potential associated ocular problems.

For example, I think that it is interesting to consider the widespread use of sildenafil and its potential effect on the pathogenesis of glaucoma in light of the subclavian steal syndrome. This syndrome was first described by Reivich and later named by Fisher in 1961. This syndrome refers to the "exercise of the arm on the side of a subclavian artery blocked proximal to the origin of the vertebral artery drawing blood from the vertebral-basilar system to the arm resulting in basilar insufficiency symptoms most notably transient weakness of the arm, headache, and even claudication of the arm."[6] It is a useful term because it briefly summarizes a complex anatomic abnormality that results in an increase in blood flow to one appendage at the expense of a more important appendage resulting in potentially dangerous physiologic effects.

Currently we think of the pathogenesis and therapy of the glaucomas not only in terms of intraocular pressure, axoplasmic flow and neuroprotective factors, but also in terms of potential changes in ocular blood flow. Therefore, it may be important for us to acknowledge the possibility of yet another syndrome: the subumbilical steal SINdrome (Flach and Shaffer,

1999). This would be defined as the progression of optic nerve damage and visual field loss despite normal intraocular pressures related to significant changes in blood flow while using sildenafil with or without concurrent vasodilators. If the existence of this syndrome proves to be clinically important, it will without doubt provide investigators interested in blood flow physiology with even greater challenges in deciding how and where to measure simultaneous increases and decreases in blood flow that might be beneficial or detrimental to the glaucomatous process.

In closing, I want to again congratulate the authors on an excellent scientific paper; by comparison, my discussion has provided little more than comic relief.

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DR WILLIAM TASMAN. Thank you for such a "stimulating" discussion.

DR ALAN M. LATIES. I want to thank Dr Flach for his "stimulating discussion." Dr Flach brought up the question of other drugs; there are some interesting parallels with other drugs." Let me just read from Dr Fraunfelder's book. "Ocular side effects after administration: problems with color vision (objects have yellow tinge; halos around objects, mainly blue or yellow; color hallucinations); decreased intraocular pressure; eyelid or conjunctival reaction." The drug in question is amyl nitrate. Thank you.